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UNIVERSITY OF ROCHESTER, SCHOOL OF MEDICINE AND DENTISTRY, N.Y.

STUDIES IN RESPIRATORY PHYSIOLOGY - CHEMISTRY AND MECHANICS OF PULMONARY VENTILATION - AND APPENDIX

FENN, W.O.; OTIS, A.B.; RAHN, H. AUG'51 559PP PHOTO, TABLES, DIAGRS, GRAPHS

WADC, RESEARCH DIV., WRIGHT-PATTERSON AIR FORCE BASE, DAYTON, O., USAF CONTR. NO. W-33-038-AC-14716 (AF TECHNICAL REPORT NO. 6523)

RESPIRATION
BREATHING, PRESSURE
GASES, RESPIRATORY
LUNGS

MEDICINE (19)
PHYSIOLOGY (2)

UNCLASSIFIED

AF TECHNICAL REPORT No. 5526 August 1951

STUDIES IN RESPIRATORY PHYSIOLOGY

Chemistry and Mechanics of Pulmonary Ventilation

Prepared By

Department of Physiology
School of Medicine and Dentistry
University of Rochester

W. O. Fenn
A. B. Otis
H. Rahn
Responsible Investigators

United States Air Force
Wright Air Development Center
Wright-Patterson Air Force Base, Dayton

AF Technical Report No. 6528

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Aero Medical Laboratory
USAF Contract W 33-038 ac-14716
E. O. No. 696-61

United States Air Force
Wright Air Development Center
Wright-Patterson Air Force Base, Dayton, Ohio

FOREWORD

The experimental investigations in respiratory physiology presented in this report were carried out in the Department of Physiology, School of Medicine and Dentistry, University of Rochester, Rochester, New York and were conducted in the majority of cases under the provisions of USAF Contract W-33-038 ac-14713 with Dr. J. W. Wilson of the Physiology Branch, Aero Medical Laboratory acting as project monitor.

ABSTRACT

Inasmuch as this technical report is the compilation of scientific papers treating a diversity of specialized aspects of the physiology of external respiration and, therefore, does not lend itself to simple, concise summarization, the contained papers have been divided into seven natural groups and a summary of each division made. These summaries are contained under the section entitled A Brief Summary of Investigations on pages ix through xiv.

PUBLICATION APPROVAL

For the Commanding General:

for Henry M. Swezey
ROBERT H. BLOUNT
Colonel, MC (USAF)
Chief, Aero Medical Laboratory
Research Division
Wright Air Development Center

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PREFACE

For many years prior to the war we had been interested, in this laboratory, in the circulatory effects of positive and negative pulmonary pressures. Nothing substantial was done about this matter until we learned of the possible importance of positive pressure as an aid to the oxygen supply at high altitudes. In 1941 with this in mind we offered to study this question for the Committee on Medical Research of the Office of Scientific Research and Development at an initial contract of $500.00 During the progress of the work we had the advantage of close association with Captain (now Colonel) Pharo Gagge at the Aeromedical Laboratory at Wright Field who was working out the practical technique for applying this method to actual flight conditions. This close association has continued to be profitable and stimulating during the succeeding eight or more years of our work on this subject.

When the O.S.R.D. was discontinued after the war Col. Gagge negotiated for us a contract with the Air Force Materiel Command which enabled us to keep our team of investigators intact and assured the continuation of our work. The contract has been ideal from the point of view of the University. We have always been encouraged to plan our own program of research and have been left free to carry it out without the slightest pressure from the Air Force. Investigators have been permitted to receive part of their salaries from the University so that a proportionate amount of time could be spent in the stimulating occupation of teaching and part of the money was utilizable for the training of graduate students who were preparing theses for the Ph.D. degree on work done under the general subject of the contract. We should like to express here our profound appreciation to the Air Force for this very wise, generous and helpful policy which has provided us with such ideal conditions for creative work.

During the progress of this work, three concepts developed which were of particular importance to us in our thinking. The first of these was the pressure volume diagram of the chest and lungs. The second was the oxygen - carbon dioxide diagram of the composition of the alveolar air and the third was the ventilation - perfusion ratio of the alveoli.

All of our work on the mechanics of breathing and the circulatory effects of pressure breathing has been carried out with reference to the pressure - volume diagram of the lungs. Relations between pulmonary pressures and blood pressures in the veins and arteries were worked out in this connection. The role of the elasticity of the lungs in absorbing some of the pulmonary pressure was clearly indicated. More recently the possibilities for studying the mechanics of respiration has been considerably expanded by a new method for measuring the pressure gradient between the mouth and the alveoli while breathing at different velocities. Equations for calculating the work of breathing have now been developed which permit a fairly accurate appraisal of the work required at different frequencies and minute volumes as well as an improved method of characterizing the breathing apparatus of different individuals in terms of chest elasticity, air flow resistance, etc. While other methods for doing this are still under exploration we feel that the field has been greatly expanded as a result of these studies.

The oxygen-carbon dioxide diagram of the alveolar air is a method of representing graphically the complicated mathematics required for the calculation of the composition of the alveolar air in terms of the composition of the inspired air, the gas exchange in the lungs of both oxygen and carbon dioxide and the volume of the ventilation. The chief complication comes from the fact that the respiratory quotient is not unity and the volumes of expired and inspired air are not exactly equal. The most valuable characteristic of the diagram is that the respiratory quotient or exchange ratio turns out to be a straight line on the chart. The application of these charts to problems of voluntary pressure breathing and acclimatization to high altitude has seemed to us to be especially helpful.

The third concept of major importance which has come out of our studies concerns the ventilation to perfusion ratio. This came simultaneously and independently from the work of Dr. Rahn in our laboratory and Dr. Riley at Bellevue Hospital. Both were able to obtain a line on the oxygen - carbon dioxide chart to represent all the possible gas compositions of the alveoli in a lung with a given inspired gas and a given mixed venous blood. Positions along this line represented different ventilation to perfusion ratios. Alveoli which were well ventilated but under-perfused lay at the end of the line near the inspired air point while, conversely, alveoli which were underventilated but over perfused lay at the end near the point of mixed venous blood. Dr. Riley has made important additions to this concept and in our own laboratory, also, it has led Dr. Rahn into further studies of the pulmonary circulation and alveolar-arterial pressure gradients.

The number of names attached to the various papers published under this program reflects fairly accurately the number of persons who have been associated with us during the eight or more years of our work. Except for the early years the actual responsibility for the organization and conduct of the work in the laboratory has been undertaken by Drs. Hermann Rahn and Arthur B. Otis. They have also been responsible for more than their full share of the new ideas which have been developed. Relatively few of the authors on the published papers have received salaries from the Air Materiel Command although the program has been generously supported in accordance with our actual needs.

For permission to reproduce in this report articles previously published we wish to make grateful acknowledgement to editors of the following journals: The American Journal of Physiology (papers Nos. 1,3,4,5,6,16,24,31,32,35,36,41,48,54, 57,58.) The Journal of Applied Physiology (papers Nos. 10,11,14,17,18,28,37,38,40,52.) 52.) The Proceedings of the Society for Experimental Biology and Medicine (papers No. 26,27,39.) The Journal of Aviation Medicine (papers Nos. 19,25,29.) The Journal of Clinical Investigation (papers Nos. 2,7.) The Review of Scientific Instruments (paper No. 30.) and the Proceedings of the American Philosophical Society (paper No. 34.)

Rochester, N. Y.
May 17, 1951

Wallace O. Fenn

A BRIEF SUMMARY OF INVESTIGATIONS

A. PRESSURE BREATHING

The mechanical effects of pressure breathing are best shown by the pressure - volume diagram of the lungs and chest. Careful measurements were made of the pulmonary relaxation pressures and the maximum inspiratory and expiratory pulmonary pressures in a series of 15 normal young men. (No. 1) Breathing was studied under both positive and negative pressure. The expiratory reserve increases as the pressure becomes more positive and decreases with negative pressures. The work of breathing against these different pressures was also calculated and was found to pass through a minimum at a positive pressure of 3.5 mm Hg. The velocity pattern of breathing as recorded in a pneumotachogram is markedly changed by pressure breathing. (No. 8).

Measurements were made of the venous pressure during pressure breathing and the results were explained in terms of the elasticity of the lung, which absorbs some of the pulmonary pressure. (No. 3) If the lung volume is maintained constant an increase in pulmonary pressure causes a nearly equal increase in the venous pressure. If the lung is allowed to expand with the increase in pulmonary pressure the venous pressure increment is correspondingly less (about 50%). In general, the venous circulation readjusts itself to different lung pressures so that the filling of the heart is not affected. With positive pressures of 30 cm H_2O in trained subjects the cardiac output decreases 14% as shown by the ballistocardiograph. (No. 7) For moderate pressures not causing circulatory failure, both systolic and diastolic arterial pressure rises or falls with corresponding changes in pulmonary pressure. In anesthetized animals positive pressure breathing stops respiration and leads to a fall in arterial pressure. (No. 2) This finding is explained in terms of a new concept of great importance to an understanding of the nervous control of respiration. Afferent impulses from the lung stimulate respiration inversely as the volume of the lung. A mere decrease in average volume constitutes a potent respiratory drive. (No. 9).

Part of the compensation for pressure breathing is a peripheral vasoconstriction. This can be demonstrated by a cooling of the finger tips, and a decrease in blood flow through the finger as measured by the plethysmograph. (No. 5, 6) A decrease in leg volume can also be demonstrated by a plethysmograph when the transmission of passive effects due to damming back of venous blood is prevented by a partially inflated pneumatic cuff. (No. 4) The feet become relatively heavier during positive pressure breathing because of a displacement of blood from the lungs which may amount to as much as 500 cc. (See also No. 55 and 56).

Intermittent pressure breathing using the pneumolator was also investigated. (No. 10) With this apparatus the pressure is increased in the lungs during inspiration only. This leads to some hyperventilation, acapnia, and excretion of base in the urine, and an increase in the alveolar oxygen tension. The alveolar oxygen tension is also increased because the mean pulmonary pressure is increased but this increase

is not so great as with continuous pressure breathing. For this reason, in most subjects, continuous PB is probably a better method of gaining altitude tolerance than intermittent PB.

In voluntary pressure breathing, the subject makes strong expiratory efforts with closed glottis before each expiration. (No. 11) This causes a small increase in the mean pulmonary and mean alveolar PO_2. It also leads to some hyperventilation. At the same time it increases the oxygen requirement because of the muscular effort involved; and the pressure developed falls rapidly with the onset of fatigue. It is concluded that the advantage derived from this maneuver is chiefly due to the hyperventilation and the consequent increase in the alveolar oxygen partial pressure.

A more detailed review of the subject of pressure breathing will be found in the reports of two talks given by one of us at conferences called by military authorities for the discussion of the subject. (Nos. 12 and 13).

B. MECHANICS OF BREATHING

One of us has recently published a review which gives a general outline of the work which we have done in this subject. (No. 15) Our studies began with the pressure - volume diagram of the chest and the lungs which has already been described. (No. 1) From published values for intrathoracic pressures in man some estimate was made of the value of the lung elasticity. The relaxation pressure curve represents the balance between elastic forces of the relaxed chest and diaphragm and the elastic recoil of the lung. Most of the work of breathing is due to the stretching of these elastic structures. In addition it is necessary to estimate the work of moving the air and distorting the tissues (tissue viscosity). Methods of estimating the work required for this purpose have been described and equations have been developed which permit the calculation of the work of breathing at any frequency and tidal volume. (No. 14).

The work of breathing is increased, of course, by artificially added resistances. (No. 19) The work of inspiration is consistently greater than the work of expiration. With added resistance the velocity of air movement and the total ventilation is diminished and the alveolar pCO_2 is increased.

The pressure difference between the alveoli and the ambient air was measured under a variety of conditions. (Nos. 16-18). This pressure difference is the sum of two factors; a viscous factor which is proportional to the velocity of flow and a turbulence factor which is proportional to the square of the velocity. The proportionality constant for the latter varies with the density of the gas and is therefore diminished at altitude and with admixture of helium at ground level. Experiments verified the theoretical expectations in both conditions. (No. 17).

More recently in our laboratory Dr. Arthur DuBois has devised a new method for studying the pressure volume diagram of the chest and lungs which promises to be very helpful. This consists in recording the respiratory loops obtained on a cathode ray oscilloscope when pressure moves the ray vertically and volume moves it horizontally. Samples of these loops are given in report No. 20. Preliminary

experiments indicate that this method may also yield a direct determination of the elasticity of the lung in the intact animal, the direct measurement of which remains one of the chief deficiencies in our present knowledge of mechanics of breathing.

At the request of the Aero-medical Laboratory we made a study of the Burns Pneumatic Valve resuscitator. This included both the physiological reactions of the patient (No. 21) and the engineering principles involved (No. 22). The latter concerned the application of the laws of air flow through small orifices and resulted in a diagrammatic description of the frequencies of cycling consistent with adequate ventilation. One of us acting in the capacity of consultant made a survey of the results of clinical studies of this apparatus carried out under contract with the Air Force in various laboratories (No. 23).

C. PERFORMANCE AT ALTITUDE

As criteria for performance we have used hand steadiness, contrast brightness discrimination, choice reaction time and time for completion of multiplication of 5-digit numbers. All of these tests show a diminished performance when the alveolar pCO_2 is decreased to 20 - 25 mm or below. (No. 25) The tests were conducted at 30,000 ft. breathing pure oxygen so that the oxygen supply was always adequate. A large number of other tests have been carried out at various altitudes up to 46,000 ft. and with different degrees of hyperventilation (pCO_2 of 12 mm or above) as obtained by the use of the pneumolator. The effect of hypoxia alone is obtained by correcting the gross performance score for the effect of the accompanying hypocapnia. Knowing thus the separate effects of hypoxia and hypocapnia, predictions can be made for each test of the expected performance at any combination of alveolar oxygen and carbon dioxide values. For each test there is an optimum alveolar pCO_2 at each altitude. It is found that hypoxia and hypocapnia are additive in their effects. (No. 24) Under ordinary conditions at altitude, without any artificial hyperventilation the diminution in performance is shown to be largely due to the hypoxia rather than to the small amount of accompanying hypocapnia.

Since hypocapnia contributes so little to the performance at altitude it is not to be expected that the additions of CO_2 to pure oxygen for inhalation would provide any benefit and this is confirmed by experiment. It changes the alveolar gas composition scarcely at all and merely means that the subject must breathe harder to maintain the same alveolar oxygen and carbon dioxide tension in the lungs. This was also demonstrated clearly by means of survival tests on mice with and without CO_2. (No. 27) When CO_2 is added to air for inhalation at altitude there is always an improvement in survival but this is due to the resulting increase in alveolar pO_2. By adding CO_2 the subject is free to increase further his ventilation and therefore his alveolar pO_2 without seriously depleting his alveolar CO_2. (Nos. 35 and 36).

In an effort to find a more objective type of performance test some observations were made on the cornea - retinal potential. (No. 28) It was found that this potential increased about 20% during hypocapnia but an increase in hypoxia occurred only in certain individuals so that the test proved unreliable as an index of performance.

In a series of experiments on mice it was demonstrated that air is preferable to pure oxygen even though the oxygen is used at such an altitude that the inspired oxygen tensions are equal in the two cases. Because of the "nitrogen dilution effect" the alveolar tension is actually higher in the case of air. (No. 26).

D. ALVEOLAR GAS EXCHANGE

We have found that the understanding and quantitative prediction of changes in the composition of the alveolar air has been greatly facilitated by the O_2-CO_2 diagram already referred to in the Preface. (No. 31) For the collection of data for such charts a simple method was devised which permits the automatic and continuous sampling and analysis of alveolar gases. (Nos. 22, 37) Combining this new experimental method with the new theoretical treatment an extensive study has been made (Nos. 35-40) of the transient changes in the alveolar air which result from various unsteady states produced by (1) acute exposure to simulated altitudes (2) exercise with various inspired oxygen and carbon dioxide concentrations (3) artificial increments of the dead space (4) breathing of different CO_2 mixtures (5) anesthesia and (6) asphyxia.

The changes in alveolar gas concentrations which occur during adaptation to and recovery from any of these stresses follow definite pathways when plotted on the oxygen-carbon dioxide diagram. These "reaction loops" always appear to move in a clockwise direction in a manner that is characteristic and predictable for each type of stress. (No. 37) More recently the analysis of these results in terms of the ventilation-perfusion equation has in part explained the exact shape of these "loops."

The ventilation perfusion equations result in what may be termed the "Ventilation/Perfusion line" on the O_2-CO_2 diagram. (No. 32) In this concept it is supposed that individual alveoli differ in their gas concentrations because of variations in their ventilation perfusion ratios. Some are well ventilated with air but poorly perfused with blood and vice versa. For a given inspired air and a given gas concentration in the mixed venous blood there is a single ventilation-perfusion line connecting these two points on the chart and passing through all the possible alveolar air concentrations which could theoretically exist. The particular point on the line which represents the actual mean alveolar air concentration can then be predicted from the R.Q. Experiment has shown that our method of sampling alveolar air (No. 37) gives values which are very close to this effective mean alveolar air point and very close, also, to the measured arterial CO_2 tension. This provides, therefore, a valuable validation of the method. (Nos. 32, 36).

A study of the respiratory acclimatization of man to hypoxic environments was carried out in Wyoming at an altitude of approximately 13,000 ft. and later at Mt. Evans at an altitude of 14,000 feet. (Nos. 36, 45). The results indicate that with acclimatization the respiratory system becomes more sensitive to CO_2. Other observations of ours combined with those of other investigators permit a fairly accurate prediction of the changes which must occur in the alveolar gas composition, arterial gases and ventilation during the process of acclimatization to any air-breathing altitude as well as during the process of reacclimatization to sea level conditions.

With the development of an instantaneous gas analyzer for various gases, particularly CO_2, it becomes possible to analyze successive fractions of a single expiration and to determine the variations in composition which occur during a single respiratory cycle (Nos. 42-45).

E. PHYSIOLOGY OF BREATH HOLDING

The physiological changes which occur with breath holding have received very little attention in the literature. The events which follow such a voluntary apnea are quite dramatic and difficult to interpret.

The alveolar air changes at the breaking point are very constant from time to time and offer a simple and convenient index for estimating the sensitivity of the respiratory center to CO_2 and O_2. In one series of experiments for instance the breath was held at inspired oxygen tensions varying from 700 to 69 mm. At high oxygen tensions it was found that the breaking point was a function of the CO_2 alone. At the oxygen tension of normal air both O_2-lack and CO_2 play a role. At very high air - breathing altitudes (low O_2 tensions) hypoxia becomes the dominant factor in determining the breaking point. (No. 48).

Acclimatization to chronic exposure at an altitude of 10,000 and 14,000 feet involves a gradually increasing sensitivity of the respiratory system to CO_2 and a reduction in the breath holding time. (Nos. 49, 36). This is probably due to a simultaneous decrease in alkali reserve. At sea level a similar increased sensitivity to CO_2 can be simulated with the ingestion of NH_4Cl which reduces the alkali reserve. (No. 51). During exercise there seems to be a decreased sensitivity to CO_2 which parallels closely the changes observed in the alveolar air and arterial blood. (No. 50).

The vasomotor changes during breath holding are equally dramatic. The heart rate is reduced while systolic and diastolic blood pressures rise in parallel fashion. This is probably induced by a progressive peripheral vasoconstriction as evidenced by a decreased blood flow rate and pulse volume of the finger. (No. 45).

F. LUNG VOLUME STUDIES

The determination of lung volume by the spirometer method is a relatively simple procedure but adequate corrections for temperature and water vapor have not always been properly applied. In spite of the tremendous literature on this subject there are many variations in vital capacity which need better documentation and interpretation.

Repeated measurements of vital capacity and residual air on the same individuals over a period of many weeks have indicated the day-to-day variability which may be expected. (No. 52) Another careful study of vital capacity was conducted to verify the reduction which is alleged to occur at altitudes. After proper correction to true anatomical volumes the results indicate (1) that the reduction is considerably less than is indicated by the literature and (2) that in any event the reduction is only trancitory. At an altitude of 14,000 feet it was found that the vital capacity soon returned to normal and then increased beyond its normal value. (No. 52).

One of the causes of variation of the vital capacity is believed to be the volume of blood stored in the lungs. Thus there is a decrease in vital capacity when the subject assumes the supine position but it was found that this loss is partially regained after 10 minutes (No. 54). This suggests some mechanism for redistributing the blood after an initial period of pooling in the lungs.

An increase in vital capacity is produced temporarily by the Valsalva maneuver (No. 55). This effect is particularly large in the supine position. The increased positive pulmonary pressure apparently displaces blood from the lungs. Similar studies with voluntary negative pressures suggest that blood is thereby drawn into the lungs and the vital capacity is slightly decreased. (No. 56). Changes in the volume of blood presumably pooled in the lungs during positive and negative pressure breathing have been deduced from studies of the simultaneously observed changes in vital capacity and residual air volumes (No. 56).

C. CONVERSION OF CO TO CO_2 IN LIVING TISSUES

This interesting reaction, first reported from this laboratory in 1933 has finally been confirmed by the use of CO containing radioactive carbon (C^{14}). When this is inhaled by mice the CO_2 produced is found to contain radioactive carbon. The same is true for the respiration of isolated tissues in respirometers (Nos. 57 and 58).

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   Am. J. Physiol. 146: 161, 1946

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W. O. Fenn

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W. O. Fenn

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17. Effect of Gas Density on Resistance to Respiratory Gas Flow in Man.

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18. Effect of Adrenaline on Resistance to Gas Flow in the Respiratory Tract and on the Vital Capacity of Normal and Asthmatic Subjects.

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19. Some Physiological Effects Resulting from Added Resistance to Respiration.

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A. B. DuBois and B. Ross

21. The Pneumatic Balance Resuscitator, 1945: The Gas Exchange and Blood Flow.

H. Rahn, A. B. Otis, Mary Hodge, M. Brontman, T. Holmes and W. O. Fenn

22. Mechanical Behavior of the Burns Pneumatic Balance Resuscitator, Sept., 1945.

W. O. Fenn, A. B. Otis and H. Rahn

23. Summary of Investigations on the Burns Pneumatic Balance Resuscitator. Submitted to the Aero-Medical Laboratory, Wright Field, Sept., 1945.

W. O. Fenn

24. Performance as Related to Composition of Alveolar Air.

A. B. Otis, H. Rahn, M. A. Epstein and W. O. Fenn
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THE PRESSURE-VOLUME DIAGRAM OF THE THORAX AND LUNG[1]

HERMANN RAHN, ARTHUR B. OTIS, LEIGH E. CHADWICK AND WALLACE O. FENN

It is remarkable that physiologists have paid so little attention in the past to the mechanics of breathing that no adequate data are now on record concerning the pressure-volume-characteristics of the chest and lungs in normal men. The literature contains innumerable investigations of the various fractions of the lung volume and the vital capacity and also a number of observations concerning the positive and negative pressures that can be exerted but these two sets of data have not been correlated. There is little indication of how the vital capacity or other lung volumes vary with pressures nor, conversely, of how the pressures vary with the volume at which they are developed. Likewise there is little information concerning the relaxation pressures at different lung volumes and the relation between these data and the venous pressure. In this paper data are presented concerning the positive and negative pressures which can be produced by voluntary effort, and a diagram which gives a comprehensive picture of all these mechanical factors. Since completing this work we have discovered similar diagrams from papers by Rohrer (1916) and Senner (1921) each based upon measurements on a single individual as well as a partially similar effort by Jacquet (1908) and Bernouilli (1911).

Three types of measurement were used for the pressure-volume diagram of the lung: (1) maximum expiratory and inspiratory pressures at different lung volumes, (2) relaxation pressures at different lung volumes, (3) vital capacities, tidal air, and inspiratory and expiratory reserves at different lung pressures.

METHODS. (1) *Maximum inspiratory and expiratory pressures.* Measurements were made with a recording mercury manometer connected to a one hole rubber stopper cut to fit one nostril. The other nostril was held closed while the subject expired or inspired with maximum force. The nose was used in preference to the mouth in order to avoid all possibility of using the cheeks. It was found to be important to keep the subject from bending over in his effort to

[1] Based on work done under contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Rochester.

exert pressure since this gives him added mechanical pressure against the thoracic cage. The pressure was developed slowly in order to avoid overshoot of the mercury and was maintained at the final level for some three seconds in order to give time for oscillations to cease before the reading was taken. This measurement was repeated three times each at different lung volumes which were determined by first exhaling to the maximum possible, then inserting in the mouth a tube to a spirometer and inhaling any desired percentage (Vo) of the vital capacity. Finally without changing the volume of air in the lungs the mouth was closed and the tube was inserted in the nostril for the recording of pressure. The lung volume read from the spirometer was corrected for the decrease resulting from the development of pressure assuming a residual air of 28 per cent of the vital capacity. Correction was made according to the formula

$$Vc = \frac{(B - 47)\,Vo - pR}{B - 47 + p} \qquad \text{(Equation 1)}$$

where Vo and Vc are the uncorrected and corrected expirable volumes respectively in per cent of vital capacity, R is the residual air, and p the extra pressure developed (either positive or negative) by active effort.

(2) *Relaxation pressures.* This measurement was carried out exactly like that described for the maximum and minimum pressures except that after the desired lung volume was obtained the subject relaxed completely with one nostril connected with a water manometer the position of which was read directly. Because the relaxation pressures were so low the corrections for pressure change were omitted as insignificant. Some subjects are unable to keep the glottis open during the measurement of the relaxation pressures and a few others are unable to relax completely especially when negative relaxation pressures are being measured. This may be due to air hunger or to involuntary spasms of the diaphragm. All such subjects were eliminated from our series.

(3) *Vital capacity and lung volumes at different lung pressures.* In this series of experiments the subject was placed either supine or sitting in a body box with the head projecting through an air tight sponge rubber collar fitted around the neck. For the supine position we used a Drinker respirator set for the maintenance of constant positive or negative pressures. For the sitting position a special "body-box" was built. The subject entered through a door on the front, pushed his head through the rubber collar and seated himself on a stool underneath. The nose was occluded and the subject breathed through a mouth piece in a closed circuit which included a recording spirometer, a CO_2 absorber, and suitable check valves to keep the air circulating. The pressure in the body box was maintained at any desired level from -30 to $+40$ cm. of water by an electrically operated valve. At intervals the subject was asked to give a maximum exhalation followed by a maximum inhalation. From the graphic record measurements were made of the vital capacity, the expiratory reserve (supplemental air or the amount which could be exhaled after the end of a normal expiration) and inspiratory reserve (complemental air or the amount which could be inhaled after the end of a normal inspiration).

In these measurements there is of course a continual change of the base line on the recording drum due to the consumption of oxygen. If it could be assumed that the oxygen consumption remains constant at different pressures it should be possible to measure from the record the immediate change in volume which results from a given change of pressure. In practice it was found that the errors involved in this assumption were too large so that we decided to measure only relative volumes. The estimate of the absolute volume change in the residual air at different pressures must depend therefore upon measurements of maximum pressures voluntarily developed at different volumes as described under (1).

Since all measurements of lung volumes were expressed as percentages of the vital capacity and were corrected for pressures above or below ambient pressures the results represent relative, actual anatomical volumes.

TABLE 1

Average maximum expiratory and inspiratory and average relaxation pressures at different lung volumes with standard deviations

MAXIMUM EXPIRATORY PRESSURES		MAXIMUM INSPIRATORY PRESSURES		RELAXATION PRESSURES	
12 male subjects		11 male subjects		14 male subjects	
Volume	Positive Pressures	Volume	Negative Pressures	Volume	Pressures
per cent	*mm. Hg*	*per cent*	*mm. Hg*	*per cent*	*mm. Hg*
9.7	41.5 ± 13.4	3.9	86.0 ± 19.5	0	−19.2 ± 6.3
25.0	52.5 ± 20.8	21.7	74.6 ± 14.1	13.9	−8.5 ± 3.5
43.8	69.6 ± 19.7	34.8	63.3 ± 15.7	31.0	−1.3 ± 4.3
60.0	90.0 ± 21.5	55.6	56.8 ± 15.6	51.0	+4.1 ± 3.0
75.0	95.3 ± 17.6	75.7	44.8 ± 14.0	72.0	+10.5 ± 4.3
83.0	107.0 ± 16.3	91.0	23.6 ± 12.9	87.0	+14.9 ± 7.3
				100.0	+20.6 ± 5.2

Observations were grouped according to lung volumes and the actual volumes within each group were averaged to give the recorded values. The groups chosen were as follows: 0%, 1–20%, 21–40%, 41–60%, 61–80%, 81–99% and 100%. All volumes are expressed in percent of the vital capacity at ambient pressure. All measurements were made in the seated position.

RESULTS. (1) *Maximum expiratory and inspiratory pressures.* All the figures obtained on 11 or 12 subjects were arbitrarily divided into class groups according to the lung volumes. The figures in table 1 represent the average pressures and volumes of all the observations within each of these groups. Individual figures are not given because it is felt that the variations in any one subject from one time to another are as great as the variations between individuals so that individual differences would not be significant unless many more measurements were made.

These average figures are plotted in figure 1 as curves *Pe* (expiratory pressures) and *Pi* (inspiratory pressures). It is evident from these curves that the expiratory pressures are larger when the chest is inflated and inspiratory pressures are larger when it is deflated. This depends upon many mechanical factors but is

partly dependent upon the fact that muscles in general can exert greater pressures when they are at greater lengths; the expiratory muscles are of course stretched on inflation and vice versa. The dotted portions of these curves indicate lack of experimental basis because of the somewhat hazardous nature of the experiments required to fill these gaps.

In table 2 the data available in the literature relative to maximum pulmonary pressures are summarized for comparison with our own values. Presumably these measurements were made at a lung volume close to the optimum, i.e., at maximum inspiration for expiratory pressures and at full expiration for inspira-

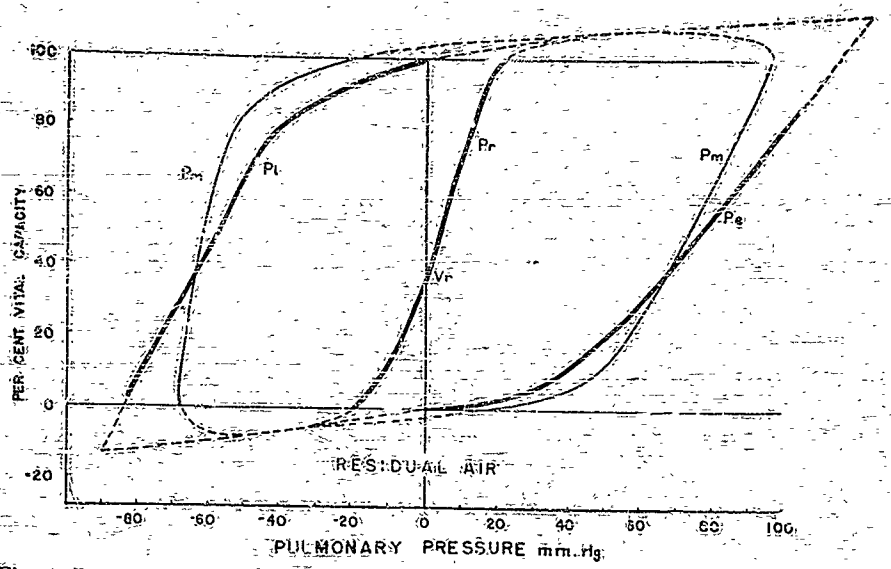

Fig. 1. Pressure-volume diagram of breathing. *Pi* and *Pe*, maximal inspiratory and expiratory pressures respectively; *Pm*, maximal pressure exerted by muscles; *Pr*, relaxation pressure; and *Vr*, relaxation volume.

tory pressures. There is apparently a paucity of data for inspiratory pressures but our values for expiratory pressures agree closely with the average.

The curve *Pr* in figure 1 represents the average relaxation pressures. Actual figures and standard errors are given in table 1 from data obtained on 14 subjects. The differences between the relaxation pressure and the active inspiratory and expiratory pressures are shown by the *Pm* curves which represent the net effect of the active contraction of the respiratory muscles.

$$Pm = Pe - Pr \text{ or } Pi - Pr \qquad \text{(Equation 2)}$$

Pr intersects the zero pressure line at the relaxation volume, *Vr*. At volumes $> Vr$, *Pr* assists the expiratory and opposes the inspiratory muscles, while at lower volumes the reverse is true. Even after making this correction for passive forces it is still true that the muscles exert more pressure when they are more

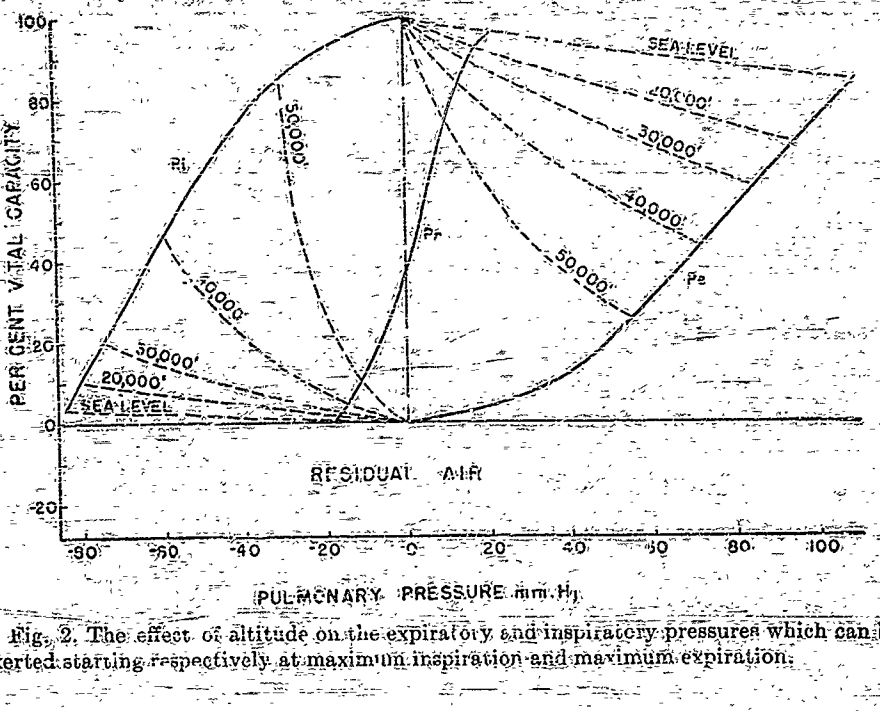

Fig. 2. The effect of altitude on the expiratory and inspiratory pressures which can be exerted starting respectively at maximum inspiration and maximum expiration.

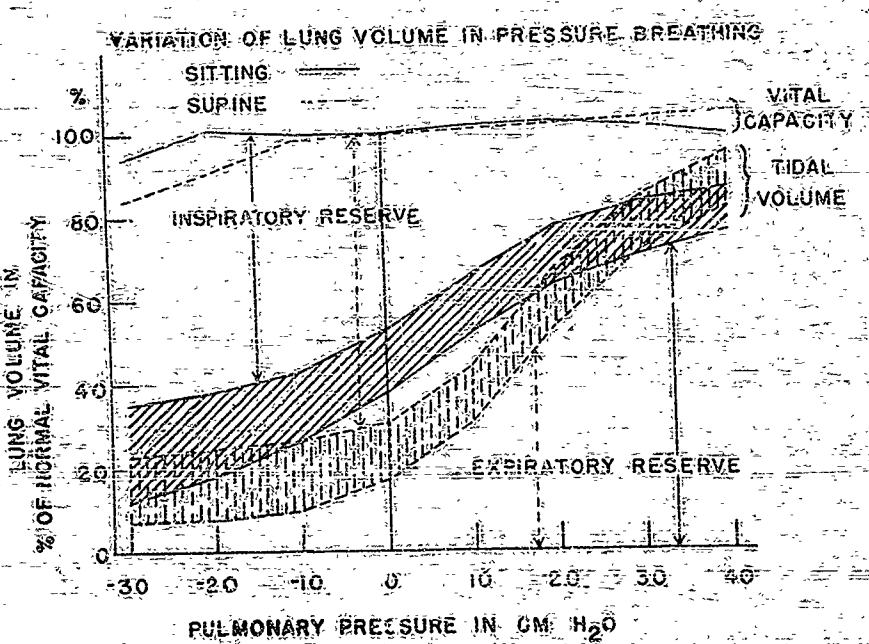

Fig. 3. Variation of lung volume in pressure breathing. The effects of intrapulmonary pressure on vital capacity, tidal volumes and expiratory and inspiratory reserves.

expected pressures have been calculated according to equation I (above) and the results are shown in figure 2. The solid lines are the same as those in figure 1 but the dotted lines represent the course which the oxygen or air would take as the subject developed pressure, starting at maximum expiration or maximum inspiration. The relaxation pressures for a given initial volume would likewise be different at altitude and the values obtained by relaxing at maximum inspiration and maximum expiration are given for each altitude by the intersection of the dotted lines with the relaxation pressure curve. At 50,000 feet the whole diagram would be very much curtailed although of course the actual mechanics of the chest are not changed at all. If additional oxygen could be added to or subtracted from the lungs as the pressure was being developed in order to prevent any change in the volume of the lung, the diagram would

TABLE 3

Average lung volumes and standard deviations, seated and supine at different pressures in per cent of vital capacity (in the seated position) at ambient pressure

Lung pressure	9–10 subjects (one ♀) seated				4 subjects (all ♂) supine			
	Vital Cap.	Expir. Res.	Tidal	Insp. Res.	Vit Cap.	Exp. Res.	Tidal	Insp. Res.
cm. H_2O	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
−30	95 ± 5	12 ± 5	23 ± 7	58 ± 12	83	7	16	60
−20	101 ± 6	19 ± 7	20 ± 5	61 ± 12	92	7	17	68
−10	100 ± 4	26 ± 4	17 ± 3	55 ± 10	99	10	17	72
0	100	38 ± 8	15 ± 3	52 ± 11	100	17	14	75
+10	102 ± 4	52 ± 9	14 ± 4	37 ± 9	102	31	13	58
+20	103 ± 5	64 ± 8	14 ± 4	25 ± 8	103	54	14	35
+30	102 ± 6	71 ± 6	13 ± 4	17 ± 5	104	72	13	19
+40	100 ± 8	77 ± 3	11 ± 6	11 ± 4	106	93	13	10

Average vital capacity at atmospheric pressure seated = 4188 cc. Exp. Res. = the volume which can be exhaled at the end of a normal expiration and Insp. Res. = the volume which can be inhaled after the end of a normal inspiration.

presumably be identical with that obtained at sea level. The corollary of this statement is that the sea level pressure-volume diagram is applicable to pressure breathing where the pressure is obtained passively rather than by voluntary effort.

(2) *Lung volumes.* The results of the measurements of the lung volumes at different pressures are summarized in table 3 where average values and standard deviations are given. The results are also plotted in figure 3. In this graph the point of maximum expiration is considered arbitrarily as zero volume at all pressures. The changes in the residual air are not therefore portrayed in the figure. It is evident that there is little change in the vital capacity in either position except for a slight decrease at the extreme negative pressures. With positive pressures up to 40 cm. H_2O it may be said that the greater expansion of the chest on inspiration is balanced by the diminished deflation on expiration so that the vital capacity remains substantially unaltered. At still higher positive

pressures the vital capacity would eventually decrease. The diminution of the expiratory reserve at zero or low pressures in the supine position as compared to the seated position is evident. A similar effect of posture is seen in the relaxation pressure curves to be described below (see fig. 6).

The data of figure 3 for the seated position have been combined with those of figure 1 in figure 4. At positive pressures the lung volumes have been added to the curve *Pe* while at negative pressures the lung volumes have been subtracted from curve *Pi*. This makes it possible to extend *Pe* (as a solid line) for a short distance into the negative pressure range and to extend *Pi* for a

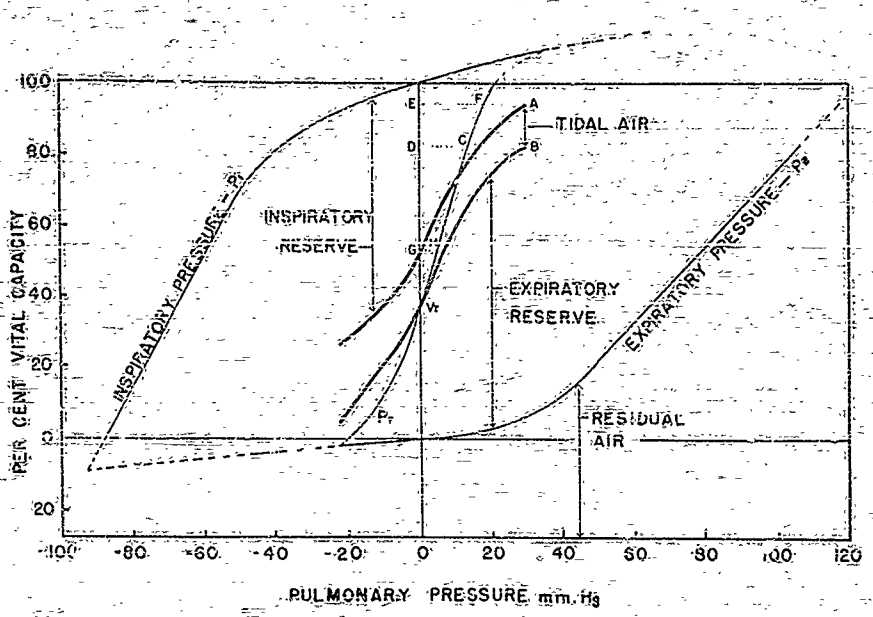

Fig. 4. Pressure-volume diagram of the lung with tidal air and relaxation pressure (*Pr* curve) added. Areas *GHVr* and *FABC* represent the elastic work of breathing at normal and 30 mm. Hg positive pressure respectively.

short distance into the positive pressure range. The actual position of the breathing range or tidal air band can be seen in relation to the relaxation pressure curve. The relaxation pressure curve is found to cut the zero pressure line at the same volume as the lower edge of the tidal air band. This is to be expected if the two sets of data are derived from the same or comparable subjects.

As the pressure increases the tidal air band is found to fall below the relaxation pressure curve and as the pressures become more negative the tidal air is found to fall above the relaxation pressure curve. This means that the respiratory reflexes do not permit the subject to relax completely on inspiration when breathing against positive pressures nor to relax completely on expiration when breathing against negative pressures. This tendency of the body to resist the pressures or to fight against them considerably increases the work of breathing.

It is also evident from figure 4 that positive pressure causes an increase in the volume of the residual air even though the vital capacity remains substantially unchanged. This has not been verified directly but the change is large enough so that further verification is hardly necessary. Many of the features of figure 4 have been confirmed in reports from the Mayo Aero-medical Laboratory under Doctor Boothby and from the Aviation Research Laboratory at Columbia University under Doctor Barach.

In 22 subjects during these experiments with the body-box, measurements were made of the frequency and depth of breathing at normal pressure and at a positive pulmonary pressure of 30 cm. of water. The average values so obtained are given in table 4 together with the rates of oxygen consumption obtained from the graphical record of the movements of the kymograph. It is evident that during the first 5 minutes of positive pressure breathing there is some hyperventilation without much change in frequency and only a small change in the rate of oxygen consumption which may or may not be significant. A small increase in metabolic rate would be expected because of the increased work of breathing.

TABLE 4

Effect of positive pressure breathing on the ventilation and metabolic rate. Average values on 22 male subjects seated in a body-box for five minutes at 30-cm. of water negative (relative positive pulmonary) pressure

PULMONARY PRESSURE	BREATHS PER MIN.	TIDAL VOL.	VENTILATION	O_2 CONSUMPTION
cm. H_2O		*cc.*	*lit./min.*	*cc./min.*
0	14	657	9.2	341
+30	16	855	13.7	356

Volumes were measured wet at room temperature and pressure.

Of the 22 men examined seven showed increases in minute volume amounting to more than 50 per cent. One of these subjects claimed to feel no discomfort and seemed otherwise normal; three felt considerable discomfort and were near the limit of endurance; three others collapsed after 5 minutes' exposure or less. All other subjects (15 men) were in good condition throughout and felt that they could have continued positive pressure breathing more or less indefinitely, though nearly all stated that they found it more fatiguing than normal breathing.

The hyperventilation shown here for pressure breathing is only an initial effect. The average subject soon adjusts himself to the new condition and his alveolar carbon dioxide tension returns to normal. The detailed evidence for this statement need not be presented here but it depends upon the fact that the average alveolar carbon dioxide tension is not changed by pressure breathing.

(3) *The relaxation pressure, Pr*, can readily be analyzed into two fractions, the lung elasticity *Pl* and the chest elasticity *Pc* where the latter includes all the elastic or gravitational factors other than those of the lungs themselves.

Then: $Pr = Pl + Pc$ (Equation 3)

The approximate relation between these quantities at different lung volumes is shown in figure 5. The evidence for this figure is indirect and requires some explanation. The lung pressures, *Pl*, will always be positive so long as the lung is not collapsed and to judge from animal experiments (Cloetta, 1913) it increases linearly over normal tidal ranges. It is assumed to be zero after all but the minimal air is expelled. The magnitude of the *Pl* may be estimated from the intrapleural pressure but care must be taken to avoid a dynamic measure which includes the head of pressure necessary to cause the air to move from the nose to

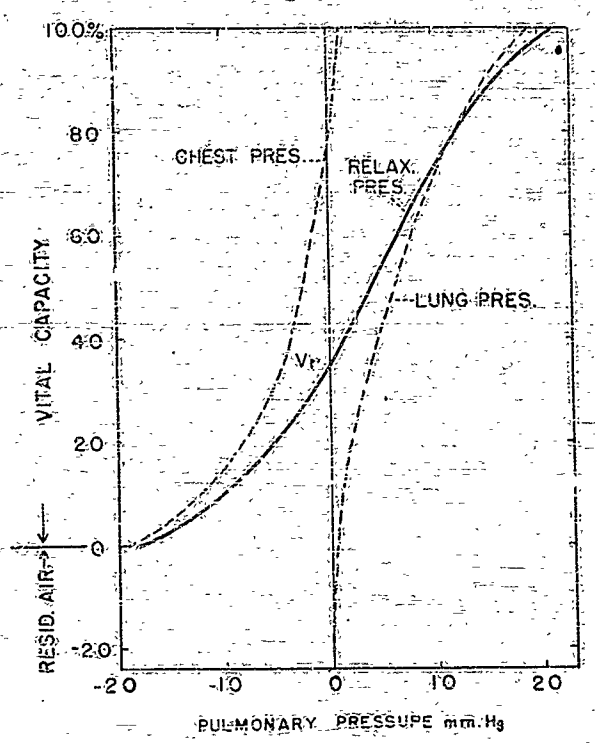

Fig. 5. The relaxation pressure curve (solid) and its two fractions (dotted), that due to the elasticity of the lungs and that due to the chest, diaphragm etc.

the alveoli (Neergaard and Wirz, 1927). From evidence of this sort the value of *Pl* at the end of a normal expiration may be taken as 4 mm. Hg.[2] Since *Pt* is zero at this point *Pc* must be −4 mm. Hg. In other words, at the end of a normal expiration the lungs are tending to collapse and the chest is tending to expand, each with a pressure of 4 mm. Hg. This is confirmed by the fact that the thoracic cage expands when the animal is given a pneumothorax (Bunta, 1936). It has been observed in patients with emphysema that the chest tends to expand due to atrophy of the elastic fibers of the lung from 40 per cent to about 72 per cent of

[2] This value has been estimated for the slightly different conditions of our experiments from the data of Bunta (1936) who recorded a value of −6 cm H_2O at the end of a normal inspiration in the recumbent position with a water manometer.

the vital capacity (Christie, 1934; Hurtado, Kaltreider, Fray, Brooks and McCann, 1934). If in these patients the Pc is normal while Pl is zero then in normal persons also the chest pressure, Pc, is zero at 72 per cent of the vital capacity. In figure 5 the chest pressure curve is drawn through this point and the lung pressure curve must then intersect the relaxation pressure curve at 72 per cent of the vital capacity. The position of this point is largely a matter of guesswork although some experimental evidence can be obtained from measurements of the venous pressure at different pulmonary pressures which will be presented elsewhere. This concept is qualitatively supported by the observation of Gerhardt (1908) that in dogs the intrapleural injection of fluids caused an expansion of the chest and a progressive fall in the intrapleural pressure until 1 liter had been injected. At this point the chest was in its neutral position and the lung was

TABLE 5

Effect of posture on the relaxation pressures at different lung volumes

LUNG VOL.	STANDING	SUPINE	DIFFERENCE
per cent	*mm. Hg*	*mm. Hg*	*mm. Hg*
	13 men		
100	21.2 ± 5.6	27.2 ± 5.9	6.0 ± 1.7
Vr = 38	0	7.5 ± 2.2	7.5 ± 2.2
0	−21.6 ± 5.9	−13.4 ± 4.3	8.2 ± 1.5
	4 women		
100	17.8	24.1	6.3
Vr	0	6.0	6.0
0*	−10.4	−3.0	7.4

* One subject only.

Vr = relaxation volume. The average value for men was 38% of the vital capacity but was not determined for the women.

Individual data for all the subjects are found in Appendix E of Committee of Aviation Medicine report No. 430 of the O.S.R.D.

nearly collapsed. In a dog one liter must represent a large fraction of the vital capacity indicating that 72 per cent for man is perhaps an underestimate.

(4). *The effect of posture* was first determined in acute experiments in which the subject was suddenly tilted from a nearly erect position into the supine position while his relaxation pressure at a given lung volume was recording on a manometer connecting to one nostril. Measurements of this sort have been made on 13 subjects at three different lung volumes: maximum inspiration, normal expiration, and maximum expiration. Upon tilting to the supine position the relaxation pressures for these three positions increased on the average 6.0 mm., 7.5 mm. and 8.2 mm. Hg respectively. The figures are given in table 5. The indications from the use of this method are that the change from the standing to the supine position merely moves the curve over to the right. A similar change was reported by Rohrer on a single subject (1916).

This change in the relaxation pressure curve is attributed to the weight of the viscera which press against the diaphragm in the supine but not in the standing position, thus increasing the pressure in the lungs. If the abdominal contents are thought of as behaving like so much fluid then the observed effect can be quantitatively predicted with reasonable accuracy. For the purpose of this calculation the abdomen can be regarded as a cylinder with an elastic membrane, the diaphragm, tied over one end. In the vertical position the pressure against this membrane is zero or negative but in the supine position the contained fluid presses against the rubber membrane, the pressure being greatest at the bottom and least at the top. If the diameter is 20 cm., which is the average figure given by Hitzenberger (1929) for the diameter of the abdomen, then the average pressure against the membrane is 10 cm. of water or 7.4 mm. Hg. This is obviously close to the value found experimentally. This pressure could, of course, be absorbed by an increased tonus of the diaphragm without change in its position. If, however, the escape of air from the lung were prevented and the chest were kept fixed in position, then this increased abdominal pressure might force the diaphragm upward, thus raising the pulmonary pressure to equal the increased abdominal pressure. The volume of the lungs and diameter of the diaphragm is such that a movement upward of only about 1 mm. would be required. It is reasonable, therefore, that the increased relaxation pressure should be about equal to the theoretical increase in abdominal pressure. If the chest expanded much with the increased pressure, the required movement of the diaphragm would be greater than 1 mm., but probably not enough greater to change its tension so as to vitiate this comparison.

At the end of a normal expiration in the sitting position the lungs come to rest at point *Vr* where the relaxation pressure curve crosses the *Y* axis in figure 5. If the subject is tilted to the supine position with the nostrils connected to a manometer so that the lung volume remains constant the pressure increases as already explained. If on the other hand the lungs are connected to a spirometer so that the pressure remains constant at the ambient value then the spirometer rises and the lung volume decreases as illustrated in figure 6. This experiment with the spirometer has been done on 29 subjects. The average displacement was 637 ± 240 cc. which represents 13.3 per cent of the average vital capacity of 4800 cc.

A similar volume change due to posture in 8 subjects is illustrated in table 6 for the positions of maximum inspiration and maximum expiration. When a subject in the standing position expires maximally into a spirometer and is then tilted into the supine position (while his expiratory efforts continue) an additional 144 cc. on the average is forced out into the recording spirometer (column A). Conversely when a subject in the supine position inhales to the limit and is then rapidly tilted into the standing position (while his inspiratory efforts continue) he finds it possible to inhale an additional 225 cc. on the average (column B). All of these observations show that in the supine position the relaxation pressure curve in figure 5 is moved downward and to the right.

In another series of experiments, an effort was made to confirm this effect of

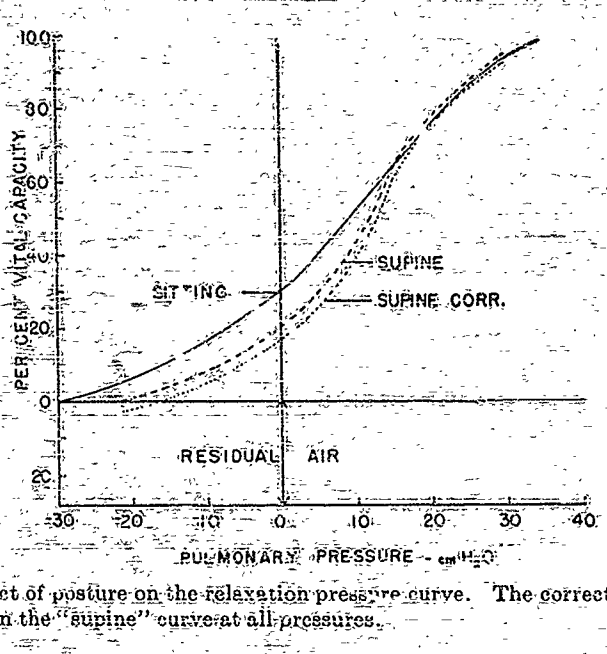

Fig. 6. Effect of posture on the relaxation pressure curve. The corrected supine curve is 3% lower than the "supine" curve at all pressures.

TABLE 6

Difference in lung volume at maximum expiration (A) and maximum inspiration (B) due to change in posture from standing to supine or the reverse

SUBJECT	POSTURAL VOLUME CHANGE		VITAL CAPACITY
	A	B	
	cc	*cc*	*liters*
1	253	260	5.68
2	170	293	4.55
3	132	120	4.81
4	90	260	5.10
5	174	226	4.40
6	193	253	4.39
7	53	80	3.79
8	86	313	4.01
Mean	141	225	4.59
% of V.C.	3.1%	4.9%	100%

Each figure presents the average of three measurements. Column A represents the additional volume expired in the supine position after tilting from the standing position at the end of a complete expiration. It is the volume decrease of the standing residual air.

Column B represents the additional volume inspired in the standing position after tilting from the supine position at the end of a complete inspiration.

posture by a different method. In these experiments, each of 10 subjects recorded his relaxation pressure in the sitting position in the usual way. Later, in the supine position, usually on the same day, the determinations were repeated.

The same posture was therefore maintained throughout the determinations of each curve and no attempt was made to tilt the subject rapidly "from a point on one curve to the corresponding point on the other".

The results of these experiments are presented in tables 7 and 8, and the averages for each of the two positions are plotted in figure 6. All of the results in the graph are expressed in per cent of the vital capacity for the sitting position. In 8 out of the 10 individuals, the vital capacity was larger in the sitting than in the supine position, but the average figures were so nearly equal (4690 cc. sitting and 4610, supine) that it makes little difference which value is used. In these experiments the fixed point arbitrarily selected for the measurement of the lung

TABLE 7

Lung volumes of 10 subjects in the sitting position at different relaxation pressures

SUBJECT	cm. H_2O																VIT. CAP.
	−35	−30	−25	−20	−15	−10	−5	0	5	10	15	20	25	30	35	40	
	Lung volumes in per cent of vital capacity																cc.
J. F.			3	7	12	19	25	30	38	48	62	74	85	90	95	99	6000
M. H.								20	32	48	60	72	84	92	100		3600
R. S.	0	3	7	10	14	19	26	36	54	68	82	91	96	100			4300
L. E. C.			0	5	11	18	26	33	46	64	78	86	93	99			4500
M. E.				2	5	8	14	21	30	39	50	63	76	85	96		5500
J. M.								34	46	57	70	86	100				4100
A. O.		3	8	12	18	24	30	36	43	50	60	73	86	96			5000
J. H.						20	23	27	31	39	50	66	82	92	100		2400
H. R.				9	16	22	28	36	47	57	66	74	83	91	98		5600
C. B.				1	8	13	17	22	34	51	68	80	88	94	100		3900
Averages	0	3	4.5	6.6	12	17.9	23.6	29.5	40.1	52.1	64.6	76.5	87.3	93.2	98.1	99	4690

Values at the particular pressures indicated were obtained by graphical interpolation.

volume in each position is the point of maximum expiration in that position. Since according to data of table 6 the residual air is less in the supine than in the erect (standing) position by 3.1 per cent of the vital capacity, the supine (dotted) curve in figure 6 has been corrected by subtracting 3 per cent from all of the values. This does not appreciably change the relative positions of the two curves. As in the comparison with the standing position the assumption of the supine position from the sitting position moves the relaxation pressure curve downward and to the right. In this case the change in volume is particularly great at the lower volumes. Attention is called to the close resemblance between these curves and the curves for the sitting and supine positions in figure 3 where the expiratory reserve varies in a similar manner. The curves of figure 6 suggest that there would be little change in relaxation pressure on going from the sitting to the supine position at maximum inspiration whereas an increase of 6 mm. Hg

was found in table 5 for the change from the standing to the supine position. This has not been verified experimentally. On the other hand the curves of figure 6 confirm the figures quoted above which show a greater volume change at *Vr* than at either maximum inspiration or maximum expiration on changing from the standing to the supine position (i.e., 637 cc. compared to 144 and 225 cc). Note that the vertical difference between the solid and dotted (corrected) curves in figure 6 a, zero pressure is very nearly equal to 637 cc.

(5) *Work of breathing.* The slope of the relaxation pressure curve at small positive pressures just above the relaxation volume is a value of some interest from

TABLE 8

Lung volumes of 10 subjects in the supine position at different relaxation pressures

SUBJECT	cm H_2O														VIT. CAP.
	−25	−20	−15	−10	−5	0	5	10	15	20	25	30	35	40	
	Lung volumes in per cent of vital capacity														cc.
J. F.	2	5	8	12	16	20	24	32	44	60	74	86	92	100	6000
M. H.	0	2	4	8	11	16	22	38	60	76	87	97			3400
R. S.	2	5	8	11	15	20	33	48	62	76	88	97			4200
L. C.		0	4	9	16	22	30	48	70	84	97				4300
M. E.				1	8	14	26	44	64	76	85	94			5800
J. M.				2	8	22	36	59	75	86	98				4000
A. O.	0	4	10	14	20	25	30	40	60	76	90	99			4900
J. H.			5	12	16	20	28	44	64	80	94				4200
H. R.		0	4	10	17	26	38	50	66	82	91	98			5500
C. B.			2	6	10	15	24	44	60	75	86	96			3800
Averages	1	2.7	5.6	8.5	13.7	20.0	29.1	44.7	62.5	77.1	89.0	95.3	100		4610
Av. in % of sitting Vit. Cap.	1	2.7	5.5	8.3	13.5	19.7	28.6	44.0	61.5	75.9	87.5	93.5	100		4690

Values at the particular pressures indicated were obtained by graphic interpolation.

the point of view of the mechanics of normal breathing. From this may be deduced the elastic work of breathing as well as the mechanical characteristics which are needed to simulate a normal chest for purposes of experimentation such as the testing of artificial respiration apparatus. This slope can be deduced from the data of tables 7 and 8 by averaging the increments of volume recorded for a change in pressure from 0 to +5 mm. Hg. For the seated position (table 7) this slope turns out to be 94 ± 35 cc. per mm. Hg. For the supine position (table 8) the corresponding value is 85 ± 31 cc. per mm. Hg. These figures correspond well with similar figures given for individual subjects by Rohrer (1916) and Senner (1921). Their values were, respectively, 107 and 97 cc. per mm. Hg.

Using our values of 94 cc. per mm. Hg for the seated position the elastic work required for an intake of 500 cc. of tidal air would be

$$500 \times \frac{500}{94} \times \frac{13.54}{10} \times \frac{1}{2} = 1800 \text{ gm. cm.}$$

This figure is in the same range as the values 1424 to 2460 gm. cm. per breath measured on dogs by Dean and Visscher (1941). This elastic work is represented by the small triangular area GHV in figure 4. The error in determining these slopes between two successive points on the curve is fairly large and the value obtained from the data on relaxation pressures given in table 1 is 180 cc. per mm. Hg. Nevertheless these data as a whole give curves very similar to those plotted from tables 7 and 8. The latter data are probably more reliable because they give lung volumes graphically determined at given pressures while in table 1 average pressures were given at average volumes within an arbitrarily selected range.

The elastic work of pressure breathing can also be calculated from the graphs of figure 4. Thus at the maximum positive pressure for which data are available (30 mm. Hg), the tidal air is represented by the line AB and the work of expira

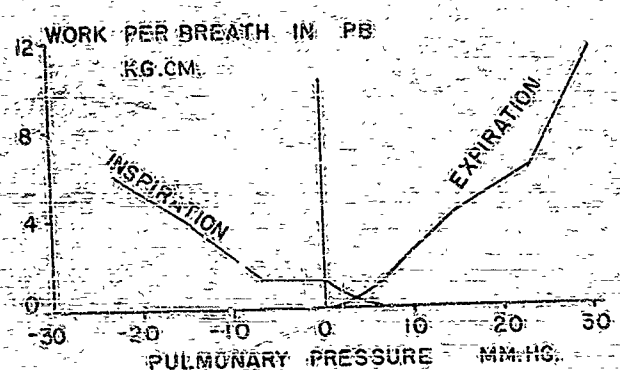

Fig. 7. The increase in the elastic work of breathing at increasing negative and positive pulmonary pressures. Figures determined graphically from areas on a diagram similar to but not identical with figure 4.

tion is given by the area $ABDE$. However, the relaxation pressure curve indicates that a part of this work could be done by elastic potential energy stored in the thoracic wall and lungs, this fraction being represented by the area $FCDE$. The net work done by active contraction of the expiratory muscles is therefore the difference between these two areas or $ABCF$. The values of these areas for different pressures have been calculated from another graph similar to that in figure 4 but differing in details, and the results are plotted in figure 7. Two curves are shown, one for inspiration and one for expiration. At zero pressure all the elastic work is inspiratory. At more negative pressures the inspiratory work increases because the chest is not allowed to relax completely on expiration.

At positive pressures the inspiratory work falls off to zero at 7.5 mm. Hg. (In fig. 4 this occurs at 10 mm. Hg where the inspiratory side of the tidal air band crosses the relaxation pressure curve.) As the pressure becomes positive however expiration becomes more and more active and the work of expiration increases, as already explained. It is an interesting point that at a pressure of about 3.5 mm. Hg half the work is inspiratory and half is expiratory and the sum

of the two is less than the inspiratory work at zero pressure. The work of breathing is therefore slightly but inconsequentially diminished by increasing the pulmonary pressure a few millimeters of Hg.

To obtain an artificial lung which will have the same elastic characteristics it is only necessary to use a rigid container having a capacity of 760 x .94 = 71 liters. We have found an ordinary kitchen hot water tank very satisfactory for the purpose.

SUMMARY

1. Average data from 10 or more individuals are presented for the construction of a pressure-volume diagram of the lung and thorax. The data consist of measurements of maximum expiratory and inspiratory pressures at different lung volumes and relaxation pressures.

2. Calculations are made to show the changes in this diagram which would result from an increase in altitude.

3. Measurements are made of the vital capacity, expiratory reserve, tidal air and inspiratory reserve in 14 individuals at 8 different pulmonary pressures ranging from 30 cm of water negative to 40 cm. of water positive. It is shown that with positive pressures the expiratory reserve (and residual air) increase, the inspiratory reserve decreases, while the tidal air and vital capacity remain approximately unaltered.

4. During pressure breathing the chest does not relax completely to the position indicated by the relaxation pressure curve so that the work of breathing is considerably increased.

5. When positive pressure breathing begins there is usually a temporary hyperventilation which disappears after 5 or 10 minutes or less. The rate of oxygen consumption is not appreciably increased.

6. The relaxation pressure curve is resolved into two components, the lung elasticity proper and the other factors (chest and diaphragm). Data are presented to indicate how these components vary with lung volume.

7. When the subject is tilted from the standing to the supine position air is expelled from the lungs amounting to 637 ± 240 cc. (if respiratory muscles are relaxed) or, if this is prevented, the pressure in the lungs rises 6 to 8 mm. Hg due to the weight of the viscera against the diaphragm. There are other factors also which modify the shape of the relaxation pressure curve in the supine as compared to the sitting position.

8. The slope of the relaxation pressure curve is such that an increase of 1 mm. Hg in the pulmonary pressure increases the lung volume by 94 ± 35 cc. The elastic work of breathing calculated from this slope is 1800 gm. cm. for a tidal volume of 500 cc.

9. In pressure breathing it is shown that a slight increase of pulmonary pressure of 3 to 5 mm. Hg results in a decrease in the work of breathing half of it being inspiratory work and half being expiratory work. With larger positive pressures or increasing negative pressures, the work of breathing increases as much as ten-fold.

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THE EFFECT OF VARYING PULMONARY PRESSURE ON THE ARTERIAL PRESSURES IN MAN AND ANESTHETIZED CATS[1]

By RAYMOND J. DERN AND WALLACE O. FENN

Numerous observations of the effects of pressure breathing on the arterial blood pressure of anesthetized animals are available in the literature (1-7). In all cases an increase in the pulmonary pressure results in a fall of the arterial pressure (mean pressure as measured on a mercury manometer), with an occasional secondary compensatory rise.

With negative pulmonary pressures the effects are less regular, according to Schaefer and Bain (2), but usually the arterial pressure rises (7). Bruns (8) showed an increased stroke volume in a plethysmographic record of a rabbit heart during negative pressure breathing and Böger, Cobet, and Stepp (9) found an increased cardiac output of 15 to 162 per cent, and an increased oxygen consumption (37 per cent) with a negative pulmonary pressure of 5 cm. H_2O in a rabbit. Since these experiments were done on anesthetized animals it is difficult to apply them directly to the human problem.

Most measurements previously made on men are confined to brief periods of increased positive pressure such as may be obtained by the Valsalva experiments (5, 6, 10-14). It has been generally found that with such an increase of intrapulmonary pressure the systemic arterial pressure rises briefly and then falls. This is followed by a secondary rise above the initial level. The secondary rise does not occur if the intrapulmonary pressure is too high. The heart rate usually accelerates. According to Bürger (13), only 3 out of 145 cases showed a slowing of the heart. Barach *et al* (15) recently reported a series of experiments on men breathing air at a constant pressure of 20 cm. H_2O in which he found a rise in arterial blood pressure equal approximately to the applied pulmonary pressure.

The effects of negative pressures in man were studied by Kuhn (16, 17) who used a mask (Saugmaske) with a restricted inlet orifice and a large outlet. Because of the increased amount of blood in the lungs this was regarded as a useful type of therapy for tuberculosis. Evidence was also offered however to show that the volume of the pulse was increased. Later, Bruns (8, 18) concluded, mostly on the basis of similar evidence, that negative pulmonary pressure increases the cardiac output. He recommended negative pressure breathing for patients with poor venous return and certain types of heart disease. Subsequent investigators have paid little attention to this subject and the treatment has not been further investigated possibly because of the danger of dilating the heart or rupturing a vein in the thorax. One such case of dilated heart was recorded by Stigler (19) as a result of negative pressure breathing (man under water breathing surface air through a tube). The evidence concerning the physiological effects of this procedure in man is still fragmentary.

The experiments reported below were designed primarily to elucidate the problems of positive pressure breathing of possible military importance, but for the sake of completeness they were extended to cover negative pressures as well. The respiratory effects of these same procedures on our subjects were studied simultaneously and the results have been reported elsewhere (20).

METHODS

For the animal experiments, cats were anesthetized with dial. Mean arterial pressures were obtained by a carotid

[1] This work was done under contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Rochester. The data included in this paper were obtained by the cooperative effort of a large group including Doctors Hermann Rahn, L. H. Chadwick, Arthur B. Otis, Lorin J. Mullins, R. E. Gosselin, and others who kindly served as subjects. Some of the other data from the same experiment have been published elsewhere (Rahn, Otis, *et al*, 1946 and Otis, Rahn, *et al*, 1946).

artery cannula connected to a recording mercury manometer.—Simultaneous right auricular pressures were recorded by means of a sound inserted to the level of the heart through the jugular vein, activating a recording tambour. Peripheral venous pressures were measured on a saline manometer connected to a femoral vein cannula. The tracheal cannula was attached to a very short sidearm on a large rubber hose. One end of the hose was connected to a compressed air line for positive pressures or to a vacuum pump for negative pressure. In either technique air was passed through the hose rapidly enough to avoid rebreathing. Pressures were regulated by a pinch clamp on the end of the hose opposite to the pump. Intratracheal pressures were measured on a water manometer connected to a sidearm in the cannula. This system permitted the pulmonary pressure to be set at any value up to 40 cm. H_2O, positive or negative, and the variation in pressure during the respiratory cycle was not over $\pm$ 3 cm. H_2O. The animal board was constructed so that the animal could be tilted either head or feet down (45 degrees) without altering the position of the heart relative to the recording instruments.

In the experiments on humans, systolic and diastolic pressures were read partly by the usual auscultatory method but more often by the use of the Tycos recording sphygmomanometer. Heart rates were counted from the carotid pulse over a 30-second interval. Measurements were made, with the subjects in the supine and in the sitting positions. In the lying position, the subjects were in a Drinker respirator and the equivalent of a positive pulmonary pressure was obtained by a continuous negative pressure in the respirator. For the sitting position we used a "body box" with the head protruding through a rubber collar in the top, or a helmet with the bottom closed by a similar collar. When the subject was in the body box or the Drinker respirator the blood pressure in the arm was recorded outside the box. In this case the pressure as read was the pressure in relation to the pulmonary or atmospheric pressure as zero, not the pressure as related to that surrounding the arm. For the sake of uniformity, therefore, we added the differential pulmonary pressure to our readings. In the charts all the pressures are those which would be read in the arm in the usual way if the positive pressure had been applied to the head only by means of a helmet. The usual procedure was to increase or decrease the pulmonary pressure in steps of 8 mm. Hg, holding the pressure at each stage for from 5 to 8 minutes.

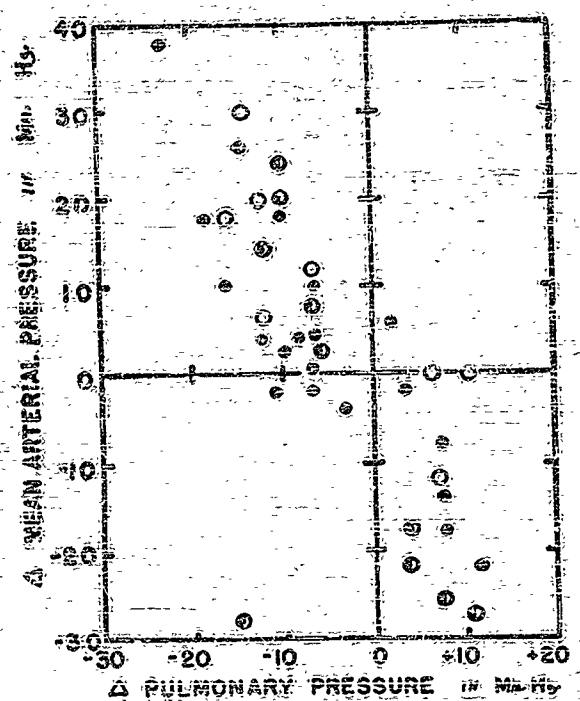

FIG. 1. THE CHANGE IN THE MEAN ARTERIAL PRESSURE OF THE CAT WHEN THE INTRAPULMONARY PRESSURE IS ALTERED

Ordinates: The change in mean arterial pressure in millimeters of mercury.

Abscissae: The change in intrapulmonary pressure in millimeters of mercury.

Meaning of symbols: Open circles: Cat in head-down position. Half closed circles: Cat in feet-down position. Solid circles: Cat in horizontal position.

RESULTS

(1) *Cat experiments.* The data of 4 cat experiments are given in Figure 1. Abscissae represent the applied intrapulmonary pressure in mm. Hg; and the ordinates, the change in mean arterial pressure. Each determination with negative pressures was made over an interval of from 1 to 5 minutes. The determinations with positive pressures are open to question since each application was brief due to threatened respiratory embarrassment and adequate time was probably not allowed for the compensatory rise found by others (2). With one exception negative pressures gave a rise in arterial pressure. With positive pressures, there is a tendency for the feet-up position to protect against a fall in arterial pressure and for the feet-down position to render the animal more susceptible to this effect. If true, this is presumably due to the effect of these positions on the venous return. The effect of negative pressures appears to be independent of the position of the animal. During the course of an experiment there was a slow but steady decline in arterial pressure. It was observed that negative pressures produced a greater rise in blood pressure if the arterial pressure was initially low, in general tending to restore the arterial pressure to normal. Shortly before

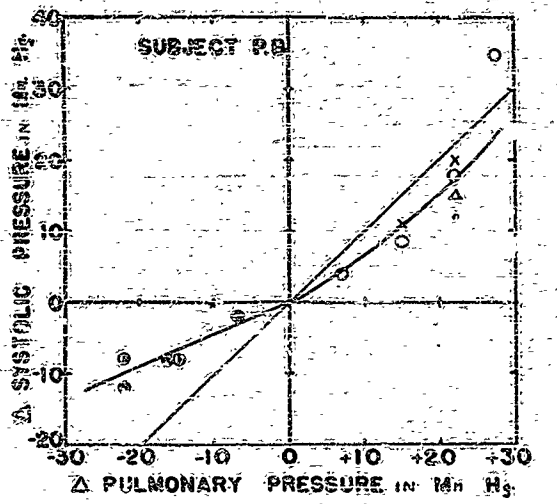

FIG. 2

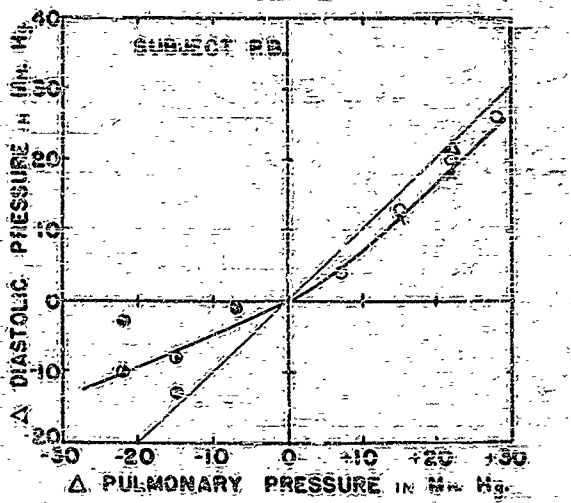

FIG. 3

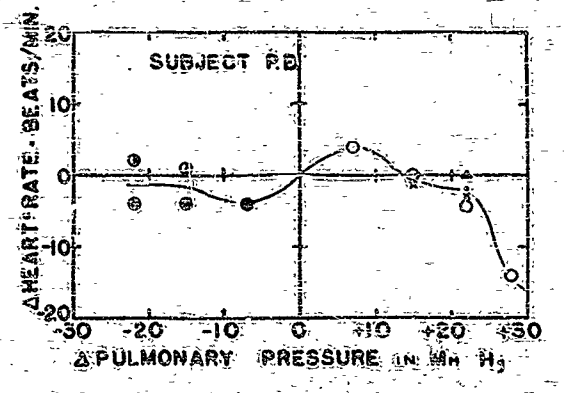

FIG. 4

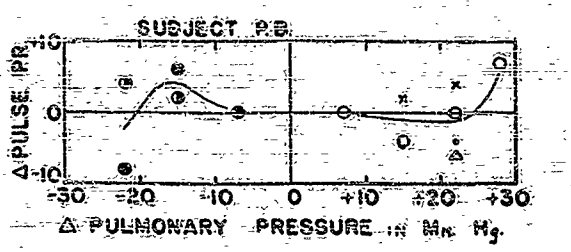

FIG. 5

FIGS. 2 through 5. The changes in systolic blood pressure in mm. Hg, diastolic blood pressure in mm. Hg, the pulse pressure in mm. Hg, and heart rate in beats per minute for one subject in the sitting position in response to changes in intrapulmonary pressures. Abscissae: The change in intrapulmonary pressure in mm. Hg.

death, however, negative pressure failed to alter the arterial pressure.

Our venous pressure data in the cat will not be presented in detail because they confirm, in general, those of Holt (21). In both cases the auricular pressure falls by an amount equal to the decrease in pulmonary pressure.[2] With increased pulmonary pressures in the dog, Holt found a rise in auricular pressure almost equal to the rise in applied pressure, but in our experiments on cats the rise was only about ½ that of the pulmonary pressure. Holt (22) and Otis *et al* (23) in their studies on man report a 50 per cent rise. The failure to obtain a greater rise has been explained by the absorption of part of the applied pulmonary pressure by the elasticity of lung tissue.

(2) *Experiments on man.* Typical results on one individual, P. B., in the sitting position are shown in Figures 2 through 5. The changes in systolic pressure are plotted against the changes in the pulmonary pressure. It is evident that the systolic pressure rose with positive and fell with negative pulmonary pressures. A change in the blood pressure equal to the change in the pulmonary pressure is indicated by the straight diagonal

[2] This equality of pressures appears to indicate that the lung is more distensible when the volume and pressure are low than in the normal breathing range.

lines passing through the origin. Since all (but one) of the points are below this line during positive pressure breathing it is evident that the systolic pressure does not follow completely the change in pulmonary pressure. However, the intrathoracic pressure does not rise quite so much as the pulmonary pressure because of the elasticity of the lungs, so it is probable that in this case the systolic pressure is closely following the intrathoracic pressure. The changes in the heart rate of P. B. (Figure 4) were variable. On some days it increased and on other days it decreased under apparently comparable conditions. Similar variations were occasionally observed in other subjects.

In Figures 6 and 7 are shown curves for systolic pressures in other individuals in the sitting and the

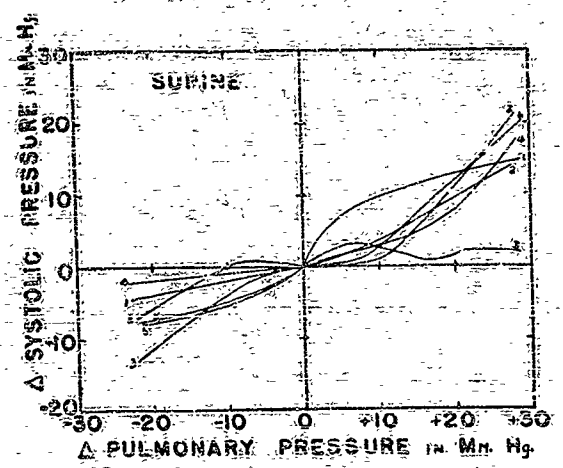

FIG. 6

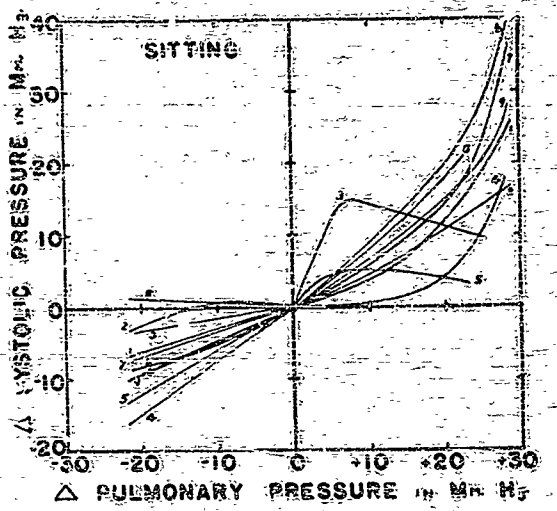

FIG. 7

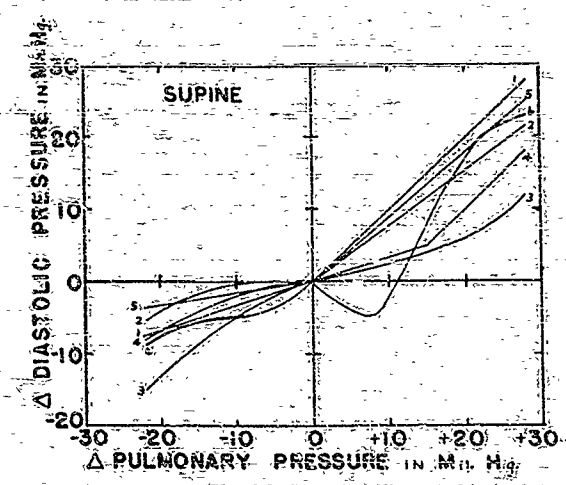

FIG. 8

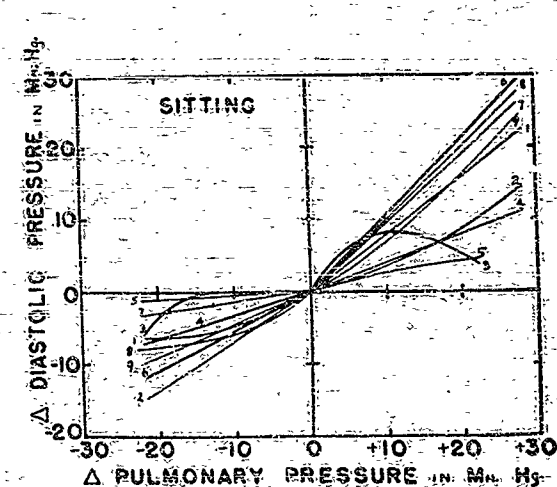

FIG. 9

FIGS. 6 through 9. The changes in systolic and diastolic blood pressure in response to a change in applied pulmonary pressure. Figures 6 and 8 are for the supine position; Figures 7 and 9 are for the sitting position. Ordinates: Figures 6 and 7, the change in systolic pressure in mm. Hg. Figures 8 and 9, the change in diastolic pressure in mm. Hg. Abscissae: The change in applied pulmonary pressure in mm. Hg. Each curve is for a single subject. Numbers on the graph identify the different subjects.

supine positions respectively. The numbers on the curves refer to the numbers of the subjects. Different subjects were used however for the two series so that similar numbers in the two series do not refer to the same subjects. All the subjects were members of the staff or medical students, and all were in normal health. The corresponding diastolic pressures in these same experiments are shown in Figures 8 and 9. The numbers of the subjects in Figures 6 and 8 correspond, as do those in Figures 7 and 9. The general result obtained in all these experiments is very evident. Positive pressures increase and negative pressures decrease both systolic and diastolic pressures. An occasional exception occurs.

The curves in Figures 6 to 9 were drawn to give a reasonable fit to the scatter of points obtained with each individual as indicated for P. B. in Figures 2 to 5. To avoid confusion the individual points are not given. Details of the curves often represent only single points and are of no significance. At the highest pressures of 20 mm. Hg the systolic pressures seem unduly high in many cases. We did not usually leave the subjects very long at this pressure and the high reading may be only an initial effect due to the excitement. When the pulmonary pressure reaches a point where the venous filling pressure is no longer able to compensate, the arterial pressure would of course be low. In subject No. 3 in the sitting position (Fig-

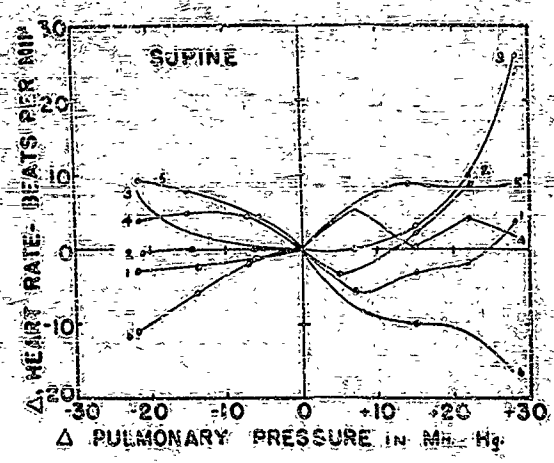

FIG. 10

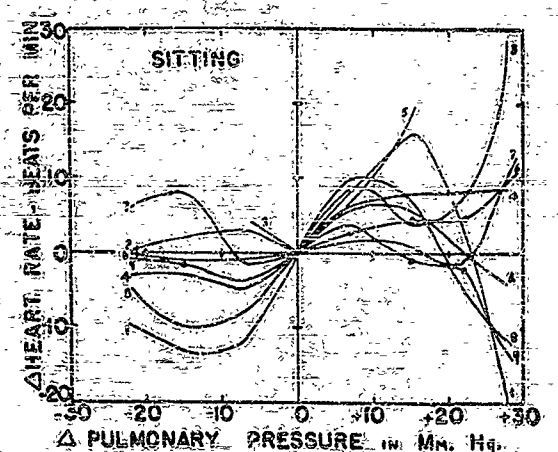

FIG. 11

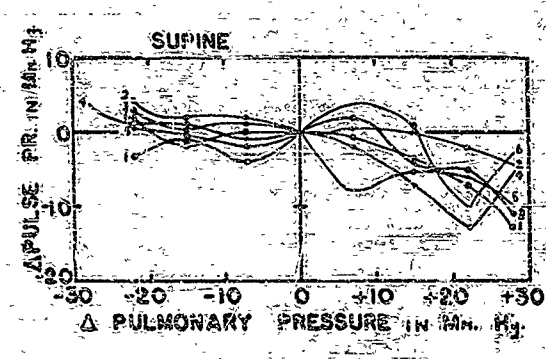

FIG. 12

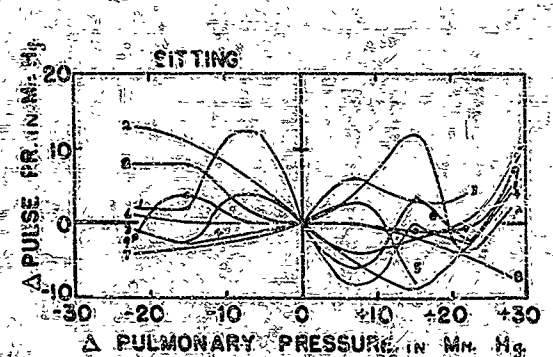

FIG. 13

Figs. 10 through 13. The change in heart rate and pulse pressure in response to a change in applied pulmonary pressure. Figures 10 and 12 are for the supine position; Figures 11 and 13 are for the sitting position. Ordinates: Figures 10 and 11, the change in heart rate in beats per minute. Figures 12 and 13, the change in pulse pressure in mm. Hg. Abscissae: The change in applied pulmonary pressure in mm. Hg. Each curve is for a single subject identified by the number on the graph

ures 7 and 9) we actually found an arterial pressure too low to give any readable deflection in the record. This occurred just before the subject had to be relieved of the pressure because of a threatened collapse. It was generally observed that the subject's blood pressure reached an equilibrium for a given pulmonary pressure within 1 minute after its application. It was also noted that in those subjects who nearly collapsed the blood pressure was maintained at its normal level until a minute or two before the onset of severe distress

A comparison of Figures 6 and 7 shows that with positive pressures the systolic blood pressure rises to a higher level in the sitting than in the supine position for an equal increment of pulmonary pressure. However, the average diastolic pressures for both positions follow roughly the intrathoracic pressure although the variation is large. This results in a decrease in the average pulse pressure in the supine position but no change in the sitting position. The various explanations suggested for these facts may be omitted here as purely speculative.

Changes in heart rate in the sitting and the supine positions are shown in Figures 10 and 11 respectively The numbers represent subjects as before. Numbers in Figures 10 and 12 correspond to those in Figures 6 and 8. In these figures the graphs are drawn through the actual points or the average points (where 2 or more observations were available). Such average points are indicated by dots on the curves. Detailed variations are of no significance, but it may be noted that, in the sitting position especially, there is a rather pronounced tendency in some subjects toward a decreased heart rate at the higher pressures. When the subject became alarmed at these high pressures or was about to collapse the rate might have gone high. (See curves for subject No. 3 in Figure 11.) Low heart rates have usually been attributed to increased intracerebral pressure and the absence of an acceleration due to excitement and effort or to a less sensitive carotid sinus which would not respond to a decreased pulse pressure. The incidence of low heart rates with increased pressure is much higher in our series than that reported by Bürger (13). Most individuals gave the same characteristic response on successive days, either a rise or a fall, but some gave an increase one day and decrease the next without apparent cause.

In the sitting position, at least, there is no consistent change in pulse pressure as can be seen from the average curves for 8 subjects shown in Figure 13. In the supine position however there appears to be a slight decrease of 10 or 15 per cent at the extreme pressure of 30 mm. Hg (Figure 12). This is consistent with the observation of a slightly decreased cardiac output (24).

DISCUSSION

Since our results with human subjects show that the arterial pressure follows approximately the intrapleural pressure (whether positive or negative) it may be argued either (1) that the explanation is purely mechanical, *i.e.* the arterial pressure is higher simply because the initial pressure in the ventricle was higher before systole began, or (2) that the blood pressure level is regulated reflexly by afferents arising from structures such as those around the aorta, which are exposed to the variations in intrapleural pressure. Such structures would respond in such a way as to maintain a constant difference between arterial and intrapleural pressure. Central structures within the brain itself would presumably behave in the same way since the pressure of the cerebrospinal fluid varies closely with the intrapleural pressure (Hamilton, Woodbury and Harper, 25). In our experiments with either helmet or body box the carotid sinus was exposed exteriorly to a pressure equal to the pulmonary pressure. If this organ were solely responsible for the regulation of the level of the arterial pressure, it would have kept the level of the blood pressure constant relative to the pulmonary pressure. Actually, the blood pressure is more nearly constant relative to intrathoracic pressure which increases somewhat more than half as much as the pulmonary pressure. Furthermore, Barach *et al* (15) have shown that when pressure is applied by mask, the arterial pressure remains constant relative to the pulmonary pressure. With their technique, the carotid sinus is not affected by the applied pulmonary pressure but is exposed through the skin to atmospheric pressure at all times. Its presumed effect would therefore be to control the arterial pressure at a level which is constant relative to atmospheric pressure. Since, in both techniques, the expected carotid sinus effect is apparently absent, it may be concluded that the carotid sinus is in-

sensitive to a rise in arterial pressure of at least 15 mm. Hg or to a fall of at least 10 mm. Hg, or that it is dominated by other receptors.

The ability of an individual to maintain pulmonary pressure has been used as a test of right ventricular fitness (6, 10, 11, 13, 26) on the theory that pressure increases the resistance of the pulmonary circuit. This is borne out by the work of Heinbecker (27) who perfused lungs in an artificial thorax. When they were inflated by negative pressure in the thorax, the flow increased but when they were inflated by positive intrapulmonary pressure the flow was decreased. No heart was included in this circuit so that inflow and outflow pressures were constant, and the result can clearly be attributed to the enlargement or diminution in the size of the vessels due to the respective increase or decrease in mean pressure surrounding them. When the heart is included in the circuit the situation is more complex because the heart is also exposed to the intrathoracic pressure. The immediate effect of pressure changes on the flow depends upon the capacity of the lungs (28, 29) which varies greatly with pressure, but in general the decrease in pulmonary resistance with negative pressure inflation is confirmed (30). In these experiments, however, the venous pressure remained constant while in the body this is not the case and the flow through the pulmonary circuit depends more upon the filling of the heart than upon the pulmonary resistance. This is especially true when the intrapulmonary pressure is maintained higher or lower than normal more or less indefinitely so that the capacity of the lung vessels can reach a steady state value.

The filling of the heart depends of course upon the venous pressure which in man appears to follow the intrapleural pressure with remarkable promptness and fidelity (23). With positive pressure the venous return is therefore well maintained, although there is evidence of a slight decrease in cardiac output (15, 24). This is indicated indirectly also by the rise of arterial pressure in man with increased intrapulmonary pressure. In the anesthetized cats, however, where the arterial pressure fell, the inflow into the heart must have diminished as it does in anesthetized dogs (31). Conversely in the cats a rise of arterial pressure was observed with negative pressure breathing indicating that the venous return was improved. In man the absence of such an increase in arterial pressure suggests that the normal venous pressure was adequate to fill the heart to its limit so that further increases of the pressure gradient had no further effect. The fall in arterial pressure which we have observed in man with negative pulmonary pressures lends no support to the idea that this procedure increases cardiac output and would therefore be beneficial, but it does not contradict this possibility. Since we have observed a diminished pulse volume during positive pressure breathing it seems probable that an increase in pulse volume occurs in negative pressure breathing as has previously been reported (17, 8, 32). Böger *et al* (9) found the heart rate decreased in anesthetized rabbits but Bruns (18) found it mostly increased in man. It is possible, therefore, that with negative pressure breathing there is a slight increase in the cardiac output just as, with positive pressure, there is, if anything, a slight decrease (15, 24). Such an increase would be particularly likely to occur in any condition in which the venous return was initially defective. Further work on the effects of negative pulmonary pressures is needed to verify this interpretation of our results.

SUMMARY

1. The response of the systolic and diastolic pressures and heart rate of man, and of the mean arterial, right auricular, and femoral venous pressures of the anesthetized cat, to increased and decreased intrapulmonary pressure was studied. Body position was also varied.

2. In the cat, mean arterial pressures rise in response to a decreased pulmonary pressure, independently of the position of the animal. With increased pulmonary pressure only the primary fall of arterial pressure was studied, and this was much less in the head down than in the feet down position. Holt's (21) venous pressure observations were confirmed.

3. In man, in both supine and sitting positions, increased intrapulmonary pressure gave an increase in both systolic and diastolic pressures, and decreased intrapulmonary pressure gave a fall in both.

4. Pulse pressures in many were variable (± 10 mm. Hg) and tended to give a consistent decrease only with positive intrapulmonary pressure in the supine position.

5. Heart rates were variable (± 10 beats per minute).

6. If increased intrapulmonary pressure produced circulatory failure, arterial pressures and heart rates were maintained until within a minute or two of the onset of severe symptoms.

7. The effect of pressure breathing on blood pressure regulatory receptors is discussed.

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VENOUS PRESSURE CHANGES ASSOCIATED WITH POSITIVE INTRAPULMONARY PRESSURES; THEIR RELATIONSHIP TO THE DISTENSIBILITY OF THE LUNG[1]

A. B. OTIS, H. RAHN AND W. O. FENN

The measurement of relaxation pressures and other static intrapulmonary pressures (Rahn, Otis, Chadwick and Fenn, 1946) has been so useful in analyzing the mechanics of respiration and especially of pressure breathing that it has seemed worth while to make simultaneous measurements of peripheral venous pressure and relaxation pressure at various lung volumes as an aid to understanding the relationship of the respiratory pressures to the circulation.

We shall present data showing how the peripheral venous pressure rises when the intrapulmonary pressure is increased by the performance of relaxation pressures and shall demonstrate that these data may be used to predict the approximate behavior of the peripheral venous pressure during positive pressure breathing. Also, we shall show how such measurements can be used to estimate the distensibility of the lungs.

Before describing these experiments it seems well to present a theoretical approach which has been useful in the analysis of our data. Let

P_p = Intrapulmonary pressure

P_L = Pressure due to lung elasticity, i.e., the lung tension. (This pressure is taken as positive in sign when tending to contract the lungs)

P_T = Intrathoracic pressure (intrapleural pressure)

P_V = Peripheral venous pressure.

All these pressures are expressed relative to atmospheric pressure as an arbitrary zero.

In the case of any static condition (chest fixed and no air moving in or out of the lungs)

$$P_T = P_p - P_L \tag{1}$$

Or if the change from one set of static conditions to another is considered

$$\Delta P_T = \Delta P_p - \Delta P_L \tag{2}$$

Since the right auricle and great veins leading to it are exposed to P_T, and since these are collapsible structures, P_V must always be slightly greater than P_T if blood is to flow into the chest from the periphery. Furthermore, if P_T is made more positive, P_V must also rise if blood is to flow in from the periphery at the same rate as before. If it is assumed that when P_T is made more positive, P_V becomes more positive by the same increment, then ΔP_T and ΔP_V may be equated, and

$$\Delta P_V = \Delta P_p - \Delta P_L \tag{3}$$

[1] Work done under contract recommended by the Committee on Medical Research between the Office of Research and Development and the University of Rochester.

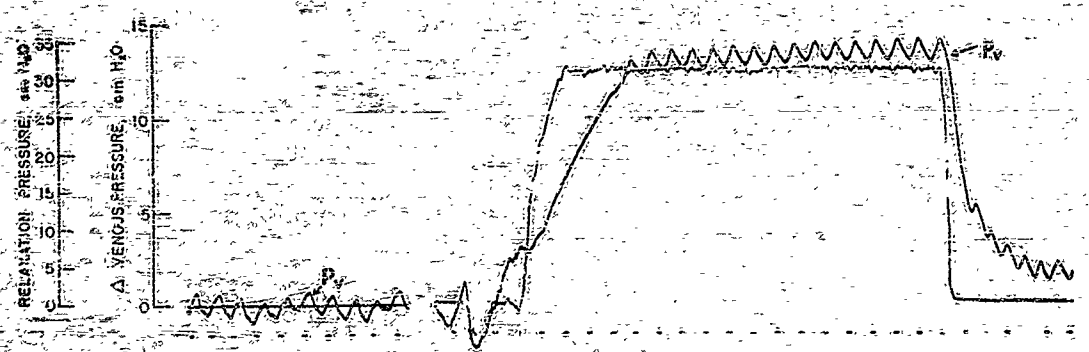

Fig. 1. At the left: record of venous pressure (P_v) variation during normal breathing. Note the venous pulse superimposed on a respiratory variation.

At the right: simultaneous record of venous pressure and intrapulmonary pressure during performance of a relaxation pressure.

Time intervals at bottom of record = 1 second. Subject, R. S.

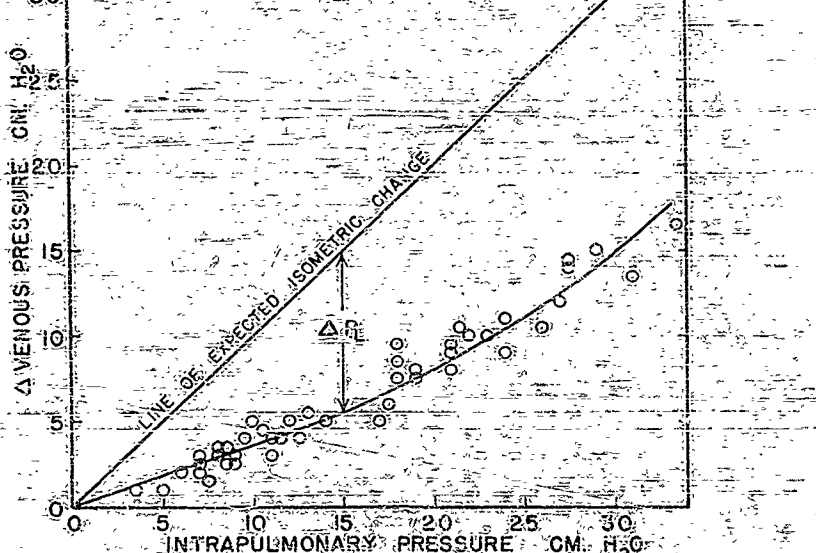

Fig. 2. The increase in peripheral venous pressure when the intrapulmonary pressure is increased by the performance of relaxation pressures.

Ordinates. Increase in peripheral venous pressure in centimeters of water.

Abscissæ. Intrapulmonary pressure in centimeters of water.

volumes other than the relaxation volume. This has been done in figure 3, using the curve of figure 2 and an average relaxation pressure curve plotted from the data of table 2 (see also fig. 7) as a basis.

The validity of two of these isometric lines, the one for the relaxation volume (about 20 per cent of the vital capacity) and the one for 100 per cent vital capacity, has been tested experimentally on two subjects who were instructed to exert pressures actively at each of these two lung volumes. The results are plotted on figure 3. The experimental points for the relaxation volume fall below the expected diagonal, whereas for 100 per cent vital capacity they are

TABLE 1

The effect of relaxation pressures on the peripheral venous pressure

SUBJECT	RELAXATION PRESSURE CM. H_2O	INCREASE IN VENOUS PRESSURE CM. H_2O	SUBJECT	RELAXATION PRESSURE CM. H_2O	INCREASE IN VENOUS PRESSURE CM. H_2O
H. R.	8.0	3.0	J. F.	18.0	7.5
	11.0	4.0		8.0	3.0
	18.0	8.5		10.0	5.0
	29.0	15.0		33.5	16.5
H. R.	6.0	2.0	M. E.	7.0	2.0
	8.5	2.5		11.5	4.0
	17.5	6.0		13.0	5.5
	26.0	10.5		12.5	4.0
				14.0	5.0
H. R.	7.0	3.0		19.0	8.0
	9.5	4.0			
	21.5	10.5	R. B.	5.0	1.0
	27.5	14.5		23.0	10.0
	18.0	9.5		21.0	8.0
	27.5	14.0		27.0	12.0
				21.0	9.0
J. McW.	3.5	1.0			
	9.0	3.0	T. H.	9.0	2.5
	22.0	10.0		18.0	7.5
	21.0	9.5		12.0	5.0
	10.5	4.5		7.5	1.5
	24.0	11.0			
			A. C.	7.0	2.0
R. S.	8.0	3.5		24.0	9.0
	8.5	2.5		17.0	5.0
	14.0	5.0		11.0	3.0
	21.0	8.0			
	31.0	13.5			
	7.0	2.5			

above the predicted line. Although the fit of the experimental points is not perfect, they demonstrate, nevertheless, that for a given increase in intrapulmonary pressure at constant lung volume, the venous pressure tends to rise by approximately the same increment.

Figure 3 is useful for predicting the approximate behavior of the peripheral venous pressure under various conditions. For example, during positive pressure breathing the mean peripheral venous pressure should vary with the mean

intrapulmonary pressure along the curve obtained from relaxation pressures, because when the positive pressure is applied, the chest tends to expand until the relaxation pressure equals the applied pressure. If the applied pressure becomes so large that it equals the maximum relaxation pressure (at maximum chest inflation) however, then any further increase in P_P will cause the venous pressure to rise along the diagonal for 100 per cent vital capacity, because further chest expansion is impossible. The data of one experiment which illustrates this are plotted in figure 3 (see points for subject M).

The effects of wearing a vest which restricts the degree to which the chest can expand may also be predicted from this graph. Suppose, for example, an individual is wearing a vest which restricts his maximum lung volume to 60 per cent of vital capacity. If 25 cm. H_2O positive pressure breathing is applied, his venous pressure will tend to rise along the curve for relaxation pressures until it intercepts the diagonal for 60 per cent vital capacity. It will then tend to follow the diagonal. The end result will be a higher venous pressure than would have been obtained without the vest. We have conducted no experiments to verify this, but Barach (personal communication) states that in 5 subjects breathing 20 cm. H_2O positive pressure the average increase in venous pressure without a vest was 41 per cent of the applied pressure and with a vest 70 per cent of the applied pressure. These data are shown plotted on the diagram in figure 3.

TABLE 2

Supine relaxation pressures at various lung volumes

SUBJECT	LUNG VOLUME AS % OF VITAL CAPACITY											VITAL CAPACITY IN CC.
	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%	
	Relaxation pressure cm. H_2O											
R. S.	−28	−12	0	4	7	11	14	18	21	26	32	4290
M. E.	−12	−3	+3	6	9	12	14	17	22	27	34	5800
J. McW.	−16	−3	0	3	6	8	10	13	17	22	27	4000
H. R.	−20	−10	−3	2	6	10	13	16	19	24	32	5500
J. F.	−27	−13	0	9	13	17	20	23	27	32	40	6000
A. C.	−15	−6	+1	6	10	13	15	17	19	23	29	5000
R. D.	−15	−8	−2	3	8	11	13	15	17	18	21	4000
T. H.	−20	−9	−1	5	8	10	12	14	16	20	25	4500
Mean	−19.1	−7.9	0.25	4.8	8.4	11.5	13.9	16.6	19.8	24.1	30.2	4875

The values for relaxation pressure in this table were obtained by interpolation from relaxation pressure-lung volume plots for each individual. The volumes were measured at room temperature saturated and are not corrected for pressure.

This venous pressure will tend to rise along the curve for relaxation pressures until it intercepts the diagonal for 60 per cent vital capacity. It will then tend to follow the diagonal. The end result will be a higher venous pressure than would have been obtained without the vest. We have conducted no experiments to verify this, but Barach (personal communication) states that in 5 subjects breathing 20 cm. H_2O positive pressure the average increase in venous pressure without a vest was 41 per cent of the applied pressure and with a vest 70 per cent of the applied pressure. These data are shown plotted on the diagram in figure 3.

The behavior of the venous pressure during a single respiratory cycle under various conditions can also be illustrated on figure 3. Consider for example a type of pressure breathing in which the intrapulmonary pressure is perfectly constant. Fluctuations in P_T and consequently in P_V would then be determined solely by the volume change in the lungs (change in lung tension), and P_V would

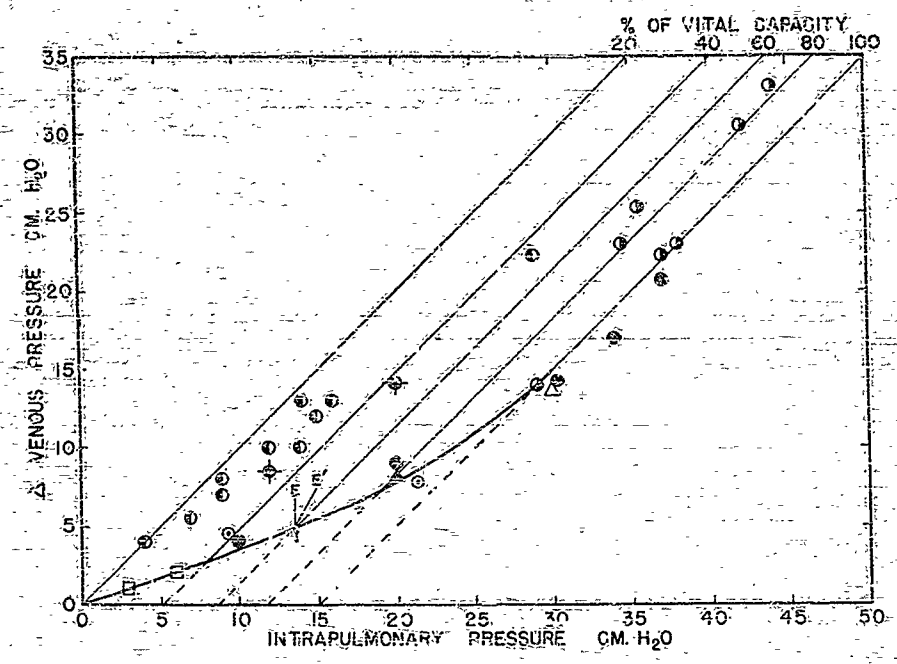

Fig. 3. Diagram showing expected changes in venous pressure with positive intrapulmonary pressure at various lung volumes.

Ordinates: Increase in venous pressure in centimeters of water.

Abscissae: Intrapulmonary pressure in centimeters of water.

Meaning of symbols:

Circle with left half closed: Change in venous pressure when the intrapulmonary pressure was voluntarily increased with the lungs held at the relaxation volume. (2 subjects)

Circle with right half closed: Change in venous pressure when the intrapulmonary pressure was voluntarily increased with the lungs fully inflated. (2 subjects)

Solid circle: Values obtained from subject M breathing various positive pressures.

Solid triangle: Mean rise in venous pressure in five of our subjects breathing a positive pressure of 20 cm. of water. The mean for Barach's subjects breathing the same pressure corresponds exactly with this point.

Open square: Mean rise in venous pressure in 10 normal individuals breathing positive pressures of 3 and 6 cm. of water. Data from Barach, Martin and Eckman (1938).

Open triangle: Mean rise in venous pressure in five of our subjects breathing a positive pressure of 30 cm. of water.

Solid circle with cross: Mean rise in venous pressure in Barach's subjects wearing a vest and breathing positive pressures of 12 or 20 cm. of water.

Circle with dot: Mean and maximum changes in venous pressure and mask pressure during breathing on the pneumolator.

be highest during expiration. The expected change in venous pressure during the respiratory cycle could be represented by a vertical straight line such as the line *I.E.* in figure 3.

Actually, of course, even so called constant pressure breathing is intermittent

since the intrapulmonary pressure is greater during expiration than during inspiration. In this case both P_P and lung volume are fluctuating and it is more difficult to predict the changes in venous pressure from moment to moment during a respiratory cycle. During expiration the lung volume will decrease and P_P will reach a maximum, during inspiration the volume will increase and P_P will attain a minimum. A possible cycle of this sort is represented by the line $I\ E'$ in figure 3.

Fluctuations of venous pressure can be observed even on a saline manometer during continuous positive pressure breathing. They may be recorded more accurately, however, by a membrane manometer such as that described above. Figure 4 shows simultaneous records of the venous pressures and mask pressures obtained during positive pressure breathing from a Pioneer pressure demand regulator. The fluctuations in venous pressure are not as large as those which

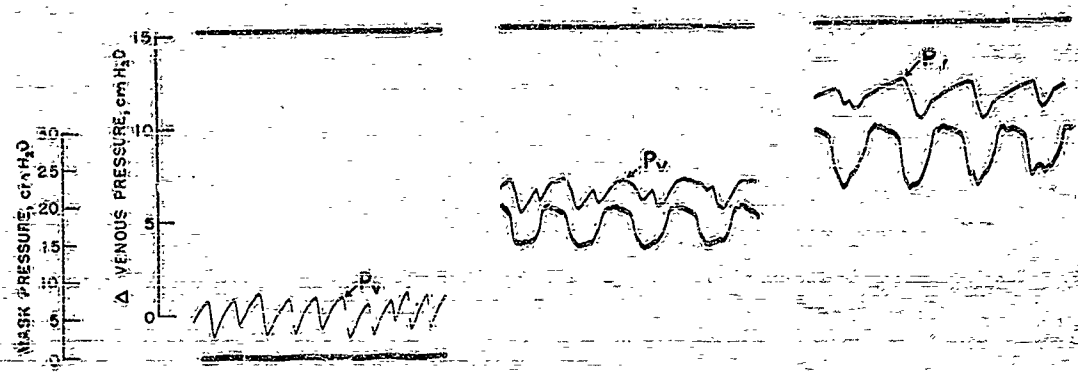

Fig. 4. At the left: record of venous pressure (P_v) during normal breathing in subject A.C.

Center and right: simultaneous records of venous pressure and mask pressure during positive pressure breathing on the Pioneer Pressure Demand valve. Time intervals at top of record = 1 second.

might be predicted. This is probably because the rate of change of P_T is too rapid for P_V to follow faithfully. This is indicated in figure 4 by the fact that the peak fluctuations in venous pressure always lag slightly behind the corresponding peaks of the mask pressure curve. It should be remembered that figure 3 is based on static measurements in which time was allowed for a steady state to be attained.

Several experiments have been performed in which subjects breathed from a pneumolator (loaned to us by the General Electric X-Ray Corporation) at various rates and pressures. A typical record from the pneumolator experiments is shown in figure 5 and a summary of the pertinent data is presented in table 3. In intermittent pressure breathing such as that which occurs with the pneumolator, the intrapulmonary pressure rises during inspiration, reaches a maximum at the peak of inspiration, and drops exponentially to zero at the end of

expiration. In this case, therefore, the venous pressure will tend to travel along the curve for relaxation pressures. Points indicating the venous pressure changes during an average respiratory cycle on the pneumolator are shown in figure 3. The agreement with the predicted values is rather good. Apparently the fluctu-

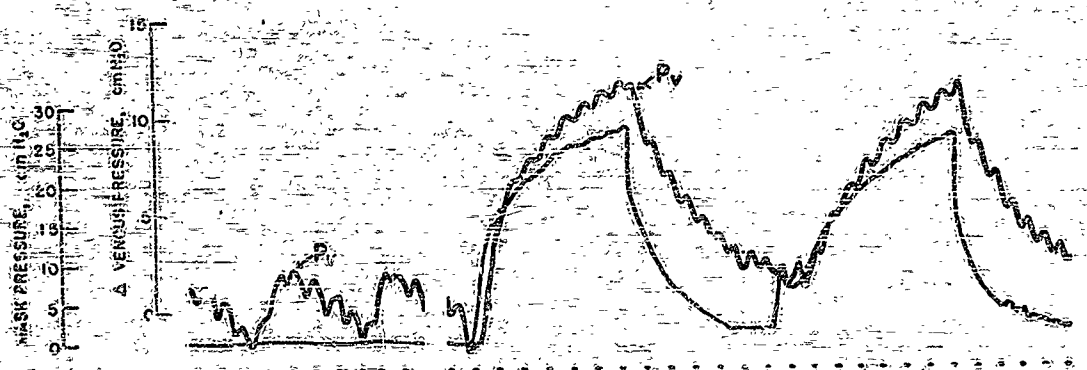

Fig. 5. At the left: record of venous pressure (P_v) during normal breathing in subject M. E. This subject, who tends to be asthmatic, shows the largest venous pressure variation with normal respiration that we have encountered.

At the right: Simultaneous record of venous pressure and mask pressure during intermittent pressure breathing on the GEX Pneumolator. Time intervals at bottom of record = 1 second.

TABLE 3

The effect of intermittent pressure breathing with the G.E.X. Pneumolator on the peripheral venous pressure

SUBJECT	MEAN MASK PRESSURE CM. H_2O	MEAN RISE IN VENOUS PRESSURE CM. H_2O	MAXIMUM MASK PRESSURE CM. H_2O	MAXIMUM RISE IN VENOUS PRESSURE CM. H_2O	FREQUENCY OF BREATHING BREATHS/ MINUTE
J. F.	12.2	3.3	25.2	6.0	6.0
H. R.	10.8	4.0	22.0	8.0	6.0
M. E.	12.3	7.4	26.0	10.6	4.6
M. E.	10.7	7.0	20.0	11.0	6.0
M. E.	5.8	3.4	16.1	6.6	10.0
M. E.	4.9	2.0	12.2	3.3	13.0
J. H.	9.2	3.8	22.5	7.3	6.0
Mean	9.4	4.5	21.4	7.7	

ations in intrathoracic pressure are slow enough under these conditions, so that the venous pressure is able to follow them with only a small lag.

Our experiments with venous pressures have been concerned only with the effects of positive intrapulmonary pressures, but Holt (1943) has measured the decrease in venous pressure associated with negative intrapulmonary pressures. The type of graph shown in figure 3 can, therefore, be extended to include the region of negative pressure. This is indicated by the dotted curve in figure 6.

The exact location of the straight line representing zero volume is in doubt, the diagram is nevertheless useful for visualizing the changes which must occur in intrathoracic and venous pressures when various sorts of breathing maneuvers are performed.

As has been suggested above, figure 3 may be used to estimate the distensibility of the lungs. For example, to determine how much the lung tension increases when the lung is expanded from the relaxation volume to 40 per cent of the vital capacity, one has only to measure the vertical distance from the 20 per cent vital capacity, one has only to measure the vertical distance from the 20 per cent isometric line to the point where the 40 per cent isometric line intersects the

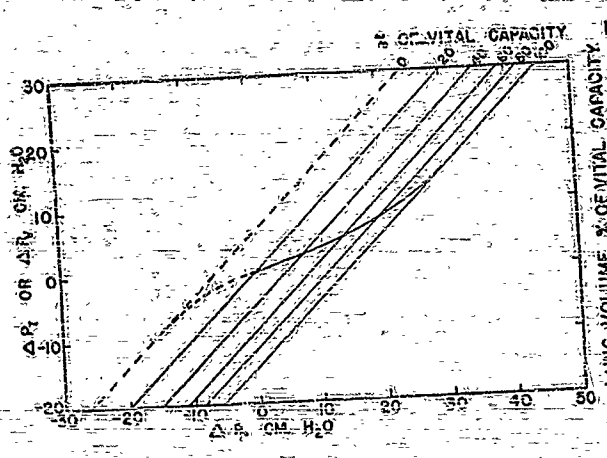

Fig. 6

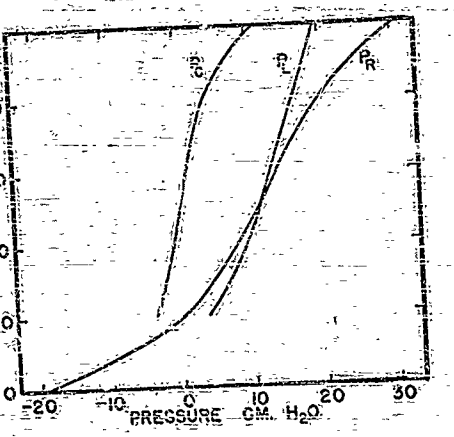

Fig. 7

Fig. 6. Extension of the diagram shown in figure 5 to include negative pressures.

Ordinates: Expected change in static intrathoracic or venous pressures in centimeters of water.

Abscissae: Static intrapulmonary pressure in centimeters of water.

Fig. 7. The relationship of relaxation pressure, lung tension, chest tension, and lung volume.

Ordinates: Lung volume as per cent of vital capacity.

Abscissae: Pressures in centimeters of water.

The relaxation pressure curve P_R was plotted from the mean values listed in table 2.

The method of obtaining the lung tension curve P_L, and the chest tension curve P_C is described in the text.

curve for venous pressure rise with relaxation pressures. The change in lung tension that occurs when the lung changes to other volumes can be determined in a similar fashion.[2] As estimated by Rahn, Otis, Chadwick and Fenn (1946) the absolute lung tension at the relaxation volume in the supine position is probably about 3 mm. Hg (ca. 4 cm. H_2O). If this value is added to the increase in lung tension that can be estimated by the above method to occur when the lungs expand from the relaxation volume to any given volume, an estimate of the

[2] The magnitude of the lung tension change with inflation from the relaxation volume to about 70% vital capacity is indicated in figure 2 by the line marked ΔP_L.

absolute lung tension at that volume is obtained. In figure 7 a curve (P_L) relating lung tensions obtained by this method to lung volumes is shown. On the same grid an average relaxation pressure curve(P_R) for the eight subjects and a chest tension curve (P_C) are drawn. The average relaxation pressure curve was obtained as indicated in table 2, and the chest tension curve was calculated from the following relationship (see Rahn, Otis, Chadwick and Fenn, 1946)

$$P_C = P_R - P_L$$

From the results obtained by Cloetta (1913) in experiments on the lungs of animals, one might expect the lung tension to show a linear variation with volume over the physiological range. The results of our experiments as interpreted in the manner described above and as plotted in figure 7 indicate, however, that P_L shows a straight line relationship with volume only above a volume represented by about 50 per cent vital capacity. Below this volume a curved function is obtained, the slope of which becomes steeper as the volume increases.

TABLE 4

Comparison of estimates of lung distensibility from various sources

INVESTIGATOR	NUMBER OF SUBJECTS	PULMONARY DISTENSIBILITY CM. H_2O PER 100 CC.
Rohrer (1915)	Based on Donders' measurements on cadavers	0.45
V. Neergaard and Wirz (1927)	1 tubercular	c. [illegible]
V. Neergaard and Wirz (1927)	1 emphysematous	0.57
Christie and McIntosh (1934)	5	1.30
Paine (1940)	8	1.13
Our Data	8	0.48

Because of the unexpected shape of our lung tension curve, one is led to look for possible errors in the method by which it was derived. One possibility is that our original assumption, viz., that a given increase in P_T produces the same increase in P_V was erroneous. Evidence for a decrease in the gradient during application of positive intrapulmonary pressure comes from the fact that the cardiac output frequently shows a decrease (Otis et al., 1946) during positive pressure breathing. We suspect therefore that the unexpected shape of our lung tension curve arises from a slight inequality between ΔP_T and ΔP_V.

Although the exact shape of this lung tension curve is of doubtful validity, it should give a value of the correct order of magnitude for the distensibility of the lungs, and it is of interest to compare the value as estimated from this curve with values obtained by other workers using different methods. If one takes the slope of the part of the curve lying between 20 and 50 per cent of the vital capacity, the lung distensibility is found to be 0.65 cm. H_2O per 100 cc. change in lung volume. The slope of the upper part of the curve gives a dis-

tensibility of 0.31 cm. H_2O per 100 cc. The arithmetic mean of these two figures gives a value of 0.48 cm. H_2O per 100 cc.

Table 4 shows that this value agrees more closely with those of Rohrer and of v. Neergaard and Wirz (1927) than with those of Christie and McIntosh (1934) and of Paine (1940). The values obtained by the latter authors are considerably larger and are subject to criticism because they are based on dynamic measurements which include not only static intrapleural pressure but also the difference between atmospheric pressure and that existing in the alveoli at the moment of measurement (i.e., the flow gradient). The values for lung distensibility by this method are probably too large. The method of v. Neergaard and Wirz should give the most valid results since it is based on the measurement of true static intrapleural pressure. However, these authors have reported measurements on only two individuals, one tubercular and one emphysematous.

It would be of interest to see the lung distensibility estimated by a method similar to ours in which simultaneous measurements of relaxation pressure and right auricular pressure were made. This would avoid the problem of a changing gradient between periphery and heart and should give more valid results. By use of the method described by Bloomfield (1945) a direct comparison could be made between values for lung distensibility estimated from measurements of intrathoracic pressure and values estimated from intra-auricular or peripheral venous pressure measurements.

SUMMARY

1. Relaxation pressures and peripheral venous pressures were simultaneously measured.

2. Data are presented to show that it is possible to predict the behavior of the mean peripheral venous pressure during various types of positive pressure breathing from the results of these measurements.

3. A method for estimating the distensibility of the lung from these measurements is discussed. A value of about 0.5 cm. H_2O per 100 cc. change in lung volume is obtained.

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DISPLACEMENT OF BLOOD FROM THE LUNGS BY PRESSURE BREATHING[1]

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The work reported in this paper was part of a study of the effects of positive pressure breathing on the peripheral circulation. A general survey of this field has been recently published by Barach, Fenn, Ferris and Schmidt (1). Evidence of decreased blood flow through the fingers has been reported elsewhere (2). This paper gives further evidence that pressure breathing causes a peripheral vasoconstriction. Furthermore, by a combination of a teeter-board and plethysmographic method an approximate calculation is made of the volume of blood (500 cc.) displaced from the lungs during pressure breathing at 30 cm. H_2O.

METHOD. The teeter-board or balance board was made of plywood on a wooden frame, *B*, 7 feet long and 2½ feet wide and was supported by knife edges, *e*, at its mid point as shown in figure 1. The subject lay supine on the board on a narrow mattress and his position was so adjusted that the foot end of the board was slightly heavier than the head end. This excess weight at the foot was supported by a steel spring attached to the board by a wire and supported on a table above the board. The spring was a flat steel strap, *S*, 9 x ⅜ x 16 inches, firmly supported at one end. Movements of the free end were magnified and recorded by a thread attachment to a heart lever, *L*, writing on a smoked drum. The foot of the teeter-board was attached by a wire close to the point of support of the spring which functioned therefore like an isometric lever. The sensitivity of this system was such that a deflection of 1 cm. on the record was produced by the addition of a 270-gram weight at the foot of the board 106 cm. from the knife edge or by a torque of 28.6 kgm. cm.

The teeter-board serves to measure the total change in torque due to the blood displaced, but does not tell precisely where the blood came from nor where it went to. To assist in the interpretation of the torque, therefore, one lower leg up to a point just below the knee was enclosed in a plethysmograph, *P*, of galvanized iron filled with air. Changes in volume of the plethysmograph were recorded by an Eberbach volume recorder, *V*, writing on a smoked drum. The sensitivity was such that a deflection of 1 cm. indicated a change in volume of 10.6 cc. The orifice of the plethysmograph was sealed airtight around the leg with plasticene and zinc ointment. This caused no interference with the venous return, and leaks could easily be detected by injecting air into the system.

[1] This work was performed under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Rochester. It was reported in December 1943 to the Committee on Aviation Medicine as Report No. 249.

This raised the recorder to a new level which was maintained constant so long as the system was airtight.

Results. *Occlusion of the venous return from the legs.* For an initial test of the apparatus, blood pressure cuffs were wound around both legs just below

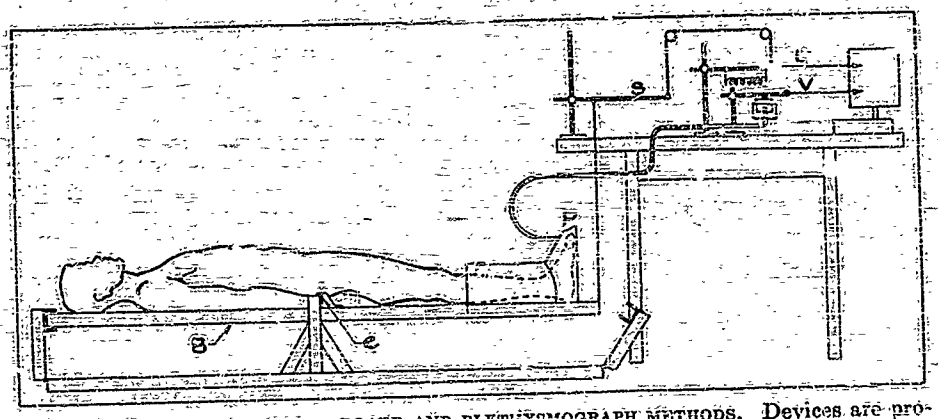

Fig. 1. Diagram of teeter-board and plethysmograph methods. Devices are provided for locking the teeter-board at both ends when not in use.

Table 1. *Effect of inflating cuff on leg*

Subject	Δ vol. in boot (a)	Δ torque (b)	Ratio, legs/foot (c)	Δ blood below cuff (d)	Distance calculated (e)	Sts. I.S. to knee (f)
	cc.	*kgm. cm.*		*grams*	*cm.*	*cm.*
Hegnauer	24.7	13.3	5.5[1]	143	93	81
Chadwick	40.6	18.6	5.0	213	87	84
Fenn	37.2	15.5	5.5	215	72	74
Rahn	39.0	17.5	4.6	188	93	90
Epstein	51.7	22.7	5.1	277	82	81
Average	38.6	17.5	5.1	207	85	82

[1] Assumed value.

Columns (a) and (b) contain the experimentally measured values resulting from the inflation of the cuff. Column (c) is the volume of both legs below the cuffs divided by a volume of the foot in the plethysmograph. The value for Hegnauer is assumed as probably nearly the same as for Fenn (measured for the others). Column (d) is the product of (a) × (c) × density of blood, 1.05. It represents the total amount of blood dammed up below the cuff if all the leg accumulates as much per liter as the foot. Column (e) is column (b) divided by column (d). Column (f) is the distance on each subject from the fifth intercostal space to the knee-joint.

the groin. When these were inflated to 60 mm. Hg pressure so as to impede the venous return, the foot plethysmograph showed an increase in volume of 38.6 cc., and the change in torque on the teeter-board was 17.5 kgm. cm. These figures are averages from 5 subjects, the individual data being included in table 1. A typical record of cuff inflation is shown in figure 2. The volume of the

legs below the cuffs and the volume of the portion of the leg in the plethysmograph were determined by water displacement and it was assumed that all the tissue in both legs below the cuff received as much blood per liter of tissue as the part in the plethysmograph. On the average then, it may be calculated that the increase in blood in the two legs below the cuffs was 207 grams (assuming a blood density of 1.05). In order to explain an increase in torque in the footward direction of 17.5 kgm. cm., 207 grams of blood must have moved an average distance of 17.5/207 or 85 cms. which is approximately the distance from the knee to the heart or lungs. The knee may be taken as the center of gravity of the legs below the cuffs, and the heart then represents the center of gravity of the origin of this volume of blood. The agreement shown in the last two columns in table 1 between this calculated distance and the measured distance from the fifth intercostal space to the knee is quite remarkable. The experiment indicates that the plethysmograph and the teeter-board agree reasonably well in their

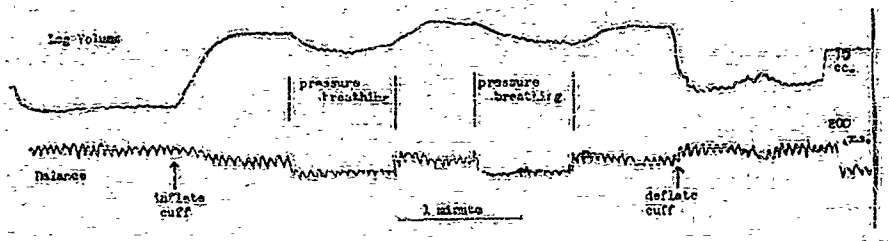

FIG. 2. EVIDENCE FOR VASOCONSTRICTION IN THE FOOT DURING PRESSURE BREATHING. When a cuff is inflated (*arrow*) around one leg the foot volume increases in the plethysmograph (*upper record*) and the foot-end of the teeter-board grows heavier (*down stroke in lower record*). With the cuff still inflated pressure breathing increases still further the weight of the foot-end of the board but the foot protected by the inflated cuff decreases in volume. At the right are calibration deflections obtained with 10 cc. and 200 grams, respectively.

readings and suggest further that the lungs act as a storage depot for blood from which supplies may be taken when any part of the normal blood volume is trapped in the periphery by venous occlusion.

Pressure breathing. In other experiments we have measured the effects of pressure breathing on the foot volume and the balance of the teeter-board. The positive pressure was applied through a pressure mask connected with a stream of air and a spring-loaded outflow valve. During the experiment the pressure was increased for a few minutes or until the circulatory response was complete, and then was released. In this procedure there seemed to be danger of an artifact because of the descent of the diaphragm during the pressure breathing. This increases the weight of the foot of the board and tends to obscure the change in weight due to the movement of blood. In order to take account of this error, we endeavored always to make readings when the diaphragm was in the same position. This was accomplished by placing two pneumographs on the subject, one around the thorax and one around the abdomen. These were attached to water manometers which were set to read zero at the end of a normal

inspiration. The manometers were placed in view of the subject. Before, during and after pressure breathing, the subject was asked to level off by expiring or inspiring until both manometers read zero. In 3 subjects, only the abdominal pneumograph was used. Measurements were made on the record from the points where this procedure was followed. The results so obtained were occasionally somewhat erratic probably because other circulatory changes were introduced in the effort to return the diaphragm to a fixed position. Thus, in one subject, expiration during pressure breathing made the feet heavier rather

TABLE 2. *Effect of pressure breathing (PB) on the volumes of the lower leg and the total balance of the body*

SUBJECT	BODY WGT. (a)	VOL. OF FOOT (b)	EFFECT OF PB		PRESSURE OF AIR BREATHED (e)	DISTANCE (f)	CALCULATED TORQUE (g)	DIFF. IN TORQUE (h)	BLOOD TO AB. (i)
			Δ vol. (c)	Δ torque (d)					
	kgm.	*% of wt.*	*cc.*	*kgm. cm.*	*cm. H_2O*	*cm.*	*kgm. cm.*	*kgm. cm.*	*grams*
Fenn	75	3.85	17.0	20.4	30	64	13.1	7.3	292
			15.1	24.8	30	64	11.7	13.1	524
			7.7	11.5[1]	20	64	6.0	5.5	220
			3.8	7.3[1]	10	64	2.9	4.4	176
			15.0	12.1	20	54	11.5	.6	24
Chadwick	72	4.2	6.6	10.6	30	67	5.4	5.2	208
Hegnauer	63	4.0[2]	15.2	24.0	30	68	12.5	11.5	460
Rahn	72	4.2	11.1	31.1	26	77	10.3	20.8	830
Epstein	79	4.2	5.0	11.5	20	65	3.9	7.6	304

Column (b) was determined by filling the plethysmograph with a measured volume of water, with and without the foot. Column (f) is an approximate estimate from the dimensions of the subject and represents the distance from the nipple line to a point on the thigh which is 0.62 the distance from the hip joint to the knee joint. Column (g) is column (c) × 1.05 (density) × 11.5 × column (f). Column (h) is column (d) minus column (g) or the torque not accounted for by blood in the lower half of the body. Column (i) is column (h) divided by 25, and represents the amount of blood which would have to move from the thorax to the abdomen (assumed distance—25 cm.) to explain the remainder of the observed torque, column (h).

[1] Abdomen tightly bandaged—successive measurements in the same experiment.

[2] Estimated.

than lighter. In any event, the method showed us that the results which we have recorded were not due merely to changes in the position of the diaphragm.

The results of these experiments are shown in table 2 for 5 subjects. With pressure breathing, there was in every case an increase in the volume of the foot and an increase in the weight of the foot end of the board. A typical record is shown in figure 3. In general, the change in torque is greatest in those subjects in whom the changes in foot volume were greatest. Considering only those cases in which a pulmonary pressure of 30 cm. of water was used, it may be said that, on the average, the foot increased 13.5 cc. in volume while the torque in the footward direction increased 19.9 kgm. cm. There was, in other words, a change of torque of 1.5 kgm. cm. for each additional cc. of blood in the foot.

When the balance was disturbed by simply blowing up the cuff without any pressure breathing (data of table 1), the increase in torque was only 0.46 kgm. cm. per cc. of blood in the foot, and this is the change in torque to be expected if, in pressure breathing, the redistribution of blood is confined to a movement of blood from the thorax to the leg below the level of the cuffs. Evidently in pressure breathing some blood also moves into regions of the body between the cuffs and the diaphragm. In order to estimate this quantity of blood, it is assumed that the foot volume indicates the amount of blood per liter of tissue which is displaced into all of the body lying below its center of gravity. According to Cotton (3), the center of gravity in men is located at a point 56.7% of the distance from the sole of the foot to the top of the head. In 4 of our subjects it was found that the volume of the foot in the plethysmograph in cubic centimeters averaged 4.1% of the body weight in grams. Taking 1.06 as the

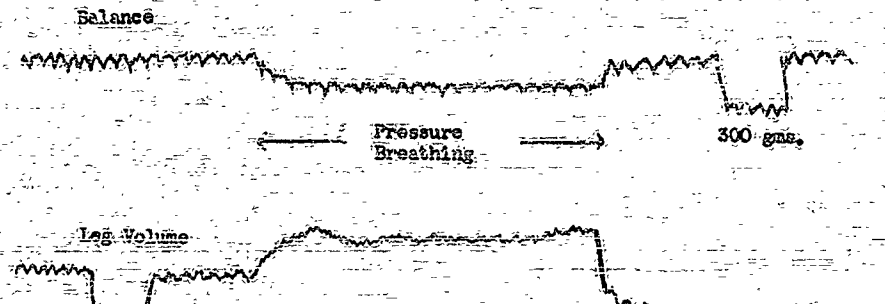

FIG. 3. PRESSURE BREATHING increases the weight of the feet (*fall in upper record*) and increases the volume of the foot in the plethysmograph (*rise in lower record*.). Calibrations are shown on both records.

density of the foot, it may be assumed that the change in blood in the lower 50% of the body is $50/(4.1 \times 1.06) = 11.5$ times as great as that in the foot plethysmograph alone. It may be assumed further that this blood comes from the thorax as it did in the experiments with the cuff alone. To estimate the distance it has moved, it is necessary to determine the location of the center of gravity of the lower half of the body. Using data for the centers of gravity of the limbs and their relative weights given by Fischer (4), we have calculated that, on the average, the center of gravity of the lower half of the body lies at a point which is 0.62 of the distance from the hip to the knee joint. The distance from that point to the mid-thoracic region averages about 69 cm. in our subjects. The change in torque to be expected, therefore, when 13.5 cc. of blood goes into the plethysmograph during pressure breathing is $13.5 \times 1.05 \times 11.5 \times 69$ or 11.2 kgm. cm. The difference (19.9 — 11.2) or 8.7 kgm. cm. must represent blood moving from the thorax to the abdomen.

In order to arrive at an estimate of the volume of blood moving from the thorax

into the abdomen, it is necessary to assume some mean figure for the distance between these two localities. This is difficult to do with any precision, but, for the sake of argument, we have used a figure of 25 cm. The amount of blood will then be 8.7/25 or 348 grams (332 cc.). With these assumptions it may be concluded, therefore, that in pressure breathing with a pressure of 30 cm. of water, 13.5 × 11.5 or 155 cc. of blood moves from the thorax into the lower half of the body including the legs, buttocks, and lower abdomen while 332 cc. moves into the abdomen.

In addition, some blood presumably goes into the head and arms. That which goes into arms would not change the torque very much because the arms lie at about the same level as the thorax, but blood going to the head would diminish the measured caudad torque. The head represents 7.06% of the body weight, and the foot in the plethysmograph about 4.1 × 1.06 or 4.35%. If the head received as much extra blood per liter of tissue during pressure breathing as the foot then the change of blood in the head would amount to $\frac{7.06 \times 13.5}{4.35}$ or 22 cc.[2] In order not to change the total torque measured during pressure breathing, it may be assumed that an equal amount of blood moved toward the abdomen an equal distance or, better, that ⅓ of this volume or 7 cc. moved toward the legs 3 times as far. In addition to this 22 + 7 = 29 cc., the arms, representing together 13% of the body weight, would receive $\frac{13 \times 13.5}{4.35}$ or 42 cc. Considering the head and arms together with the abdomen and legs, therefore, the total blood displaced from the thorax probably amounted to 155 + 332 + 29 + 42 or 558 cc. (plus or minus perhaps 200 cc.).

In one individual a series of different pressures was tried (see table 2). The data are insufficient for quantitative purposes, but it seems likely that the amount of blood displaced will be more or less proportional to the pressure. In this same experiment, the abdomen was tightly bandaged so that abdominal breathing was difficult, if not impossible. This was done to avoid artifacts due to variations in the position of the diaphragm. Thoracic breathing by itself has little effect upon the balance of the body, but may tip it headwards slightly during inspiration. The results of this experiment, however, were in no way different from those obtained without such a bandage. In one other individual, in a preliminary experiment not listed in the tables, the abdominal binding was also used with identical results. We feel convinced, therefore, that our results are not due to the displacement of the viscera by pressure breathing. This possibility is also ruled out by the precautions which we took to return the diaphragm to its normal position in taking our readings.

The water plethysmograph. This estimate which we have made of the amount of blood displaced from the lungs suffers somewhat from the assumption that

[2] This is certainly not a strictly valid assumption because the head is largely inextensible, but some blood must go toward the head and accumulate in the face, scalp, neck or shoulders, and this calculation will at least serve to show the order of magnitude of the blood involved in this process.

the foot is representative of the whole lower half of the body. In an attempt to check the validity of this point, we arranged to measure directly the increase in volume of the lower half of the body by immersing the subject in water up to the waist in an oil drum. To increase the sensitivity, a plaster of Paris cover was made which occupied most of the free surface of the water so that the addition of 100 cc. of water raised the total level by about 2 mm. The water level was observed in a glass siphon tube and scale hanging over the edge of the drum. Unfortunately, it was found impossible to include the abdomen below the water level without introducing serious disturbances due to changes in the volume and shape of the abdomen when pressure breathing was initiated. We had to content ourselves, therefore, with immersion of the legs up to the groin.

TABLE 3. *Leg volume in barrel during pressure breathing*

SUBJECT	TEMP. OF WATER (a)	PB (b)	VOL. OF LEGS IMMERSED (c)	Δ WATER LEVEL 100 cc. (d)	Δ WATER LEVEL PB (e)	Δ VOL. OF BLOOD (f)	Δ BLOOD Barrel (g)	Δ BLOOD Boot (h)
	°C.	cm. H_2O	liters	cm.	cm.	cc.	cc/liter	
Fenn	21	30	22	.27	.21	78	3.5	5.5
Rahn	21	30	18	.18	.03	17	.9	3.7
Rahn	35	30	18	.25	.16	64	3.6	
Chadwick	35.6	30	20.7	.21	.067	32	1.5	
Chadwick	28.5	30	20.7	.26	.103	39.6	1.9	
Chadwick	22	30	20.7	.24	.104	43.4	2.1	2.2

Column (b) is the pressure applied to the lungs to cause the displacement of blood. Column (c) is the amount of water which had to be added to the barrel to bring the level back to the same point after the removal of the subject. Column (d) is the increase in level caused by adding 100 cc. of water when the subject was in position, and column (e) is the corresponding rise caused by the onset of pressure breathing. Column (f) is the ratio of (e) to (d) times 100. Column (g) is the ratio of (f) to (c) or the calculated amount of blood which was displaced into each liter of leg below the water line during pressure breathing. Column (h) is a corresponding figure from the boot plethysmograph experiments for comparison.

The results of these experiments are shown in table 3. The changes in level which resulted from pressure breathing at 30 cm. of water were only 1 or 2 mm., but they were uniformly in the same direction and indicated an increase in volume by 2.3 cc. per liter of leg. The magnitude of this increase varied considerably in different individuals. Subject R was tried on two different days. A very small change was noted on the first day with the water in the barrel at about 21°C., but on the second day, at 35°C., the change was four times as large. On subject C, three different temperatures were tried on the same day, and slightly larger values were found at the lower temperatures. The last column in table 3 shows the volume increase in cc. per liter of tissue at comparable temperatures in the boot plethysmograph. These figures are to be compared with corresponding figures in the preceding column obtained by the barrel method which, on the whole, are somewhat smaller in magnitude. This dif-

ference can probably be attributed to the pressure of the water in the barrel method and the vertical instead of the supine posture. In the standing position, less blood is stored in the lungs and more in the feet. On account of these differences in the conditions, the barrel experiments do not offer much assistance in the quantitative interpretation of our other determinations, but there is certainly no indication that the blood which moves into the upper leg during pressure breathing has been underestimated.

Vasoconstriction due to pressure breathing. In all our subjects, we investigated the effects of pressure breathing while the blood pressure cuffs around both legs were inflated to 60 mm. Hg pressure. The results are interesting because they afford very clear and definite evidence of vasoconstriction in the legs as

TABLE 4. *Pressure breathing with cuff inflated*

SUBJECT	Δ VOL. IN BOOT (a)	Δ TORQUE (b)	PB (c)	Δ VOLUME BELOW CUFF (d)	CALC'D. TORQUE (e)	DIFF. IN TORQUE (f)	Δ VOL. ABOVE CUFF (g)	Δ VOL. FROM THORAX (h)
	cc.	*kgm. cm.*	*cm. H₂O*	*grams*	*kgm. cm.*	*kgm. c.m.*	*cc.*	*cc.*
Hegnauer	−7.4	6.7	30	−43	−3.4	10.1	296	253
Chadwick	−3.2	6.6	30	−17	−1.4	3.0	234	217
Fenn	−5.0	11.0	30	−29	−2.1	13.1	384	355
Rahn	−4.7	18.2	20	−23	−2.1	20.3	595	572
Epstein	−14.3	9.1	20	−77	−6.2	15.3	450	373
Average	−6.9	10.3		−38	−3.1	13.4	392	354

Columns (a) and (b) are measured values when P.B. is applied after swelling of foot due to inflation of the cuff to 60 mm. Hg is complete. Column (c) is the pressure of the P.B. Column (d) is the product of (a) and 1.05 and the leg/foot ratio from column (c), table 1. Column (e) is the product of (d) and the measured distance from the mid-thorax to the knee as given in column (b), table 1. Column (f) is (b) minus (e). Column (g) is (f) divided by an assumed distance of 34 cm. representing the distance from the mid-thorax to the center of gravity of that part of the body between the diaphragm and the top of the cuff. Column (h) is the algebraic sum of (d) and (g) and represents the net amount of blood displaced from the thorax in the direction of the feet.

a result of pressure breathing, for, at the onset of P.B. with the cuffs previously inflated, the plethysmograph always showed in all our subjects a decrease in volume which averaged 6.9 cc. or about 2.2 cc. per liter of leg (table 4, col. (a), and fig. 2). When the cuff is inflated, the increase of pressure in the central veins cannot be transmitted beyond the cuff so that there is no passive increase in volume to obscure the decrease which occurs because of the vasoconstriction.[3] The vasoconstriction outlasts the pressure breathing when the pulmonary pressure returns to normal, the lag being about 20 or 30 seconds. This same

[3] This is admittedly an assumption. Our attempts to measure the effect of pressure breathing on the venous pressure below the cuff have not been technically successful. It is not likely, however, that the venous pressure could rise much above the level of the cuff pressure without a considerable dilation and decrease in resistance to flow in the vessels under the cuff.

vasoconstriction reflex apparently occurs also when the cuff is not inflated because the immediate decrease in volume of the leg at the termination of pressure breathing is always greater than the increase in volume at the onset of pressure breathing. The difference between these two volumes is usually about equal to the decrease in volume due to pressure breathing applied while the cuff is inflated. The passive inflation of the leg due to the increased venous pressure terminates almost immediately after the pulmonary pressure falls to normal, and then the vasoconstrictor tone which still persists can cause a further temporary decrease in volume before the vasoconstriction disappears and the leg volume returns to normal. This reflex decrease in volume[4] may possibly represent a constriction of the veins which would serve to raise the venous pressure to compensate for the increased pulmonary pressure. The afferent impulses might originate from the auricle or large veins. A constriction of arterioles, however, cannot be ruled out as an equally possible explanation.

From the change in torque observed during pressure breathing with the cuff inflated (table 4, col. (b)), it is possible to estimate the amount of blood which left the thorax under these conditions. To do this it is necessary to make allowance for the calculated change in torque due to the vasoconstriction in the legs. This has been done in table 4, and the last column shows that, on the average, 354 cc. of blood left the thorax and accumulated in the abdomen and buttocks. This is in fair agreement with the estimate of 332 cc. which was reached from the data of table 2.

In conclusion, it may be said that the experiments with the cuffs inflated are of interest because they demonstrate directly that pressure breathing can still increase the caudad torque due to displacement of blood toward the feet even when movement into the legs is precluded by pneumatic cuffs. This proves directly that there is some movement of blood into the abdomen.

Torque due to pressure breathing with and without venous return occluded. Still another basis for estimating the amount of blood displaced from the lungs is furnished by a comparison of the torques produced by pressure with and without the cuffs inflated, i.e., by a comparison of the torques of table 4 with those of table 2. The pertinent data are included in table 5.

It is evident that in all 5 subjects the change in torque is appreciably greater when the cuff is not blown up (cf. col. (a) and (b)). These changes in torque represent shifts of blood which occur in addition to those shifts due to merely blowing up the cuff. They are not complicated, therefore, by removal of blood from under the cuff itself.[5] On the average, the measured change in torque was 18.4 kgm. cm. without the cuff and only 10.3 kgm. with the cuff. The difference is 8.1 kgm. cm., and this must represent the effect of blood displaced from the

[4] A similar decrease in volume might conceivably be produced by a fall in arterial blood pressure but our measurements (5) have shown that the blood pressure is increased by pressure breathing.

[5] More recent experiments by Dr. Vincent deLalla have shown that a sudden inflation of the cuffs to a pressure above the systolic level causes an increase in the weight of the head-end of the teeter board. This is of the right order of magnitude to be due to cephalad displacement of blood under the cuff itself.

thorax to the legs below the cuffs. If this distance be taken as 76 cm. as an average, then the amount of blood moved is 108 grams or about 6 cc. per liter of leg. This figure is in reasonably good agreement with the values measured in the plethysmograph, i.e., 13.5 cc. in about 3 liters of foot or 4.5 cc. per liter.

Subsequent experiments. After the completion of the original report of this work some further experiments of a similar sort were tried, partly by students in our physiology course and partly by Mr. M. Brontman. These experiments confirmed the original findings qualitatively so far as the plethysmograph was concerned; the teeter-board records were mostly unsatisfactory technically in the few cases in which they were attempted. Mr. Brontman listed 19 records

TABLE 5. *Pressure breathing with and without a cuff on the legs*

SUBJECT	TORQUE, L. E. TO FB			DISTANCE	Δ BLOOD BELOW CUFF	Δ BLOOD ABOVE CUFF	TOTAL BLOOD FROM THORAX
	With cuff (a)	Without cuff (b)	Difference (c)	(d)	(e)	(f)	(g)
	kgm. cm.	*kgm. cm.*	*kgm. cm.*	*cm.*	*grams*	*grams*	*grams*
Hegnauer	6.7	24.0	17.3	81	214	195	409
Chadwick	6.6	10.6	4.0	84	48	192	240
Fenn	11.0	20.4	9.4	74	127	320	447
Rahn	18.2	25.4	7.2	90	80	530	610
Epstein	9.1	11.5	2.4	81	30	267	297
Average	10.3	18.4	8.1	82	100	301	401

Column (c) is the difference between columns (a) and (b) and represents the Δ torque due to blood moved from the thorax to the leg below the knee. The mean distance this blood presumably moved is shown in column (d) taken from column (f), table 1. Column (e) is column (c) divided by column (d) and measures the weight of blood moved from the thorax to the legs. Column (f) is column (a) divided by an assumed distance of movement of 34 cm. which is a rough estimate of the mean distance from the thorax to the midpoint of the abdomen and buttocks, or that part of the body between the diaphragm and the cuffs on the legs. This represents the weight of blood moved from the thorax to the abdomen and hips, and explains the torque measured during pressure breathing when blood cannot accummulate in the legs because of the inflated cuffs. Column (g) is the sum of columns (e) and (f).

of pressure breathing at 15–20 cm. H_2O on 7 different subjects with a cuff on the leg above the plethysmograph at a pressure of 30–60 mm. Hg. All of these showed vasoconstriction varying from 2 to 50 cc. with an average of 5.5 cc. This agrees well with the figure of 6.9 cc. reported in table 4. In this series, in most cases a vasoconstriction was also obtained without the pneumatic cuff. This would indicate a decrease in volume in spite of the passive dilation expected from the increased venous pressure.

This discrepancy is possibly due to winding the cuff too tightly around the leg so that it protects the leg from passive dilation even before it is inflated. This also may occur when the trousers are rolled up too tightly above the knee. In any event all these experiments confirm the existence of a peripheral vasoconstriction in the foot when pressure breathing begins.

Discussion. These experiments and calculations are only approximations, but we feel that all important errors and artifacts have been eliminated so that the values reported are of the right order of magnitude. Due to errors involved in guessing distances moved, the actual amount of blood displaced may be in error by perhaps 25% or more, but, in round numbers, the measurements show that in the supine position pressure breathing at 30 cm. of water drives 500–600 cc. or 8–10% of the blood volume out of the lungs, about 3% of the blood volume going into the extremities and the remainder into the abdomen.

According to Best and Taylor (6), the lungs normally contain 9% of the blood volume during inspiration and 6% during expiration, but Kuno (7) has shown that they may contain as much as 20% under special conditions. The supine position offers a favorable condition for such an accumulation of blood in the lungs, and Cotton (3) has shown that for 20 minutes after assuming this position the weight of the cephalic end of the body continues to increase as blood returns to the thorax from the legs. The change in torque due to this process which Cotton observed in a supine subject after staircase running was 32.5 kgm. cm. In comparison with this figure, our value of 19.9 kgm. cm. for the change of torque due to pressure breathing seems not excessive. If this estimate is correct, it seems reasonable to suppose that pressure breathing in the supine position at 30 cm. of water could displace half of the blood in the lungs or about 10% of the total blood volume.

The vasoconstriction which we have observed by the boot plethysmograph in a limb protected from passive volume changes by an inflated cuff affords a most objective confirmation of the deduction made from the decreased blood flow in the finger which we have reported (2). Whether this vasoconstriction is a prolonged or merely a transient phenomenon coincident with the onset of pressure breathing is not determined by these experiments. The technique used for this observation is worthy of emphasis because so many vasoconstrictor effects of drugs or other procedures may likewise be obscured by passive venous pressure changes and this offers a ready means of separating these effects.

SUMMARY

Simultaneous measurements were made during pressure breathing of the increase in volume of the lower leg which was enclosed in a plethysmograph and of the increase in weight of the caudal end of the body as indicated by the change in balance of a teeter-board on which the subject lay supine. From these results it may be calculated that an increase of pulmonary pressure of 30 cm. of water displaces 500 cc., or about half of the blood contained in the lungs; this represents about 8 to 10% of the total blood volume. About 3% of the total blood volume goes into the extremities and the remainder into the abdomen. In the standing position, there is less blood in the lungs, and the amount which can be displaced by pressure breathing is correspondingly less.

By the use of a boot plethysmograph it is shown that the onset of pressure breathing causes an increase in foot volume due to passive inflation of the veins. If these passive changes are avoided by the previous inflation of a pneumatic

EFFECT OF PRESSURE BREATHING ON BLOOD FLOW THROUGH THE FINGER

WALLACE O. FENN AND LEIGH E. CHADWICK

This work to be reported in this paper was done in 1942[1] at a time when positive pressure breathing (PPB) showed promise of military importance as a means of raising the alveolar oxygen tension at high altitudes. Although the results are not so complete as might be desired it seems worthwhile to put them on record because of the novelty of the recording method used and the general physiological implications of the results, which indicate a vasoconstriction during PPB.

METHOD. The finger plethysmograph (fig. 1A) consisted of a light brass sleeve, *b*, terminating at one end in a $\frac{3}{16}$-inch tube and fitting loosely at the other end over the two distal phalanges of the finger. This sleeve was made airtight against the finger by zinc ointment. Volume changes were recorded by a sensitive optical tambour, *c*, and were easily calibrated by a syringe connected into the system by a T-tube. In order to record blood flow by Burton's method (1) a pneumatic cuff, *a*, was adjusted over the base of the finger. This cuff was inflated suddenly by opening the connection to a 2-liter reservoir filled with air at the desired pressure. Since the pressure in the cuff is not necessarily the pressure which is applied to the subcutaneous tissues, the proper pressure was selected by trial as the pressure which caused the maximum rate of filling of the finger. The cuff was made from a brass tube slightly larger in diameter than the finger and about $\frac{5}{8}$ inch wide (fig. 1B). Into a hole through one side of this tube was soldered a short piece of brass tube $\frac{3}{16}$ inch in diameter. A tube of thin rubber about the diameter of the brass ring was passed through the ring and the ends were turned back over the outside of the brass ring on both sides and fastened securely with adhesive tape. The annular space between the rubber tube and the brass ring could then be inflated through the small side tube and so that its pressure was applied to the finger inside.

In using this apparatus we found that inflation of the cuff produced an artifact which appeared as an increase in finger volume even when all blood flow in the arm was stopped by a pneumatic cuff around the upper arm inflated to a pressure above the systolic level. For quantitative purposes therefore it was necessary to evaluate the cuff artifact in this way during complete stasis and subtract this correction from all the observed results. In practice we used an average of 20 such determinations.

[1] This work was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Rochester. See Report No. 111 under Committee on Aviation Medicine, submitted December 18, 1942.

Measurement of the blood flow was facilitated and made graphic by the device shown in figure 1A. This is essentially a method of obstructing the recording light beam a given interval of time after the pressure is admitted to the cuff so that the height of the excursion in the optical record is a direct measure of the rate of blood flow. When the clamp, *C*, is squeezed this releases the tube, *t*, leading from the pressure reservoir to the finger cuff. At the same time it pulls a pin, *p*, which releases a weight, *w*. The weight sinks slowly in a test tube full of oil or water. After falling a fixed distance it exerts tension on a heart lever, *L*, by means of a thread. On the end of the lever is a flag, *F*, which rises and cuts off the recording beam of light. As soon as the light is obstructed, the operator releases the cuff pressure, opens the plethysmograph to the air, raises the weight and resets the apparatus for another test. These tests can be repeated

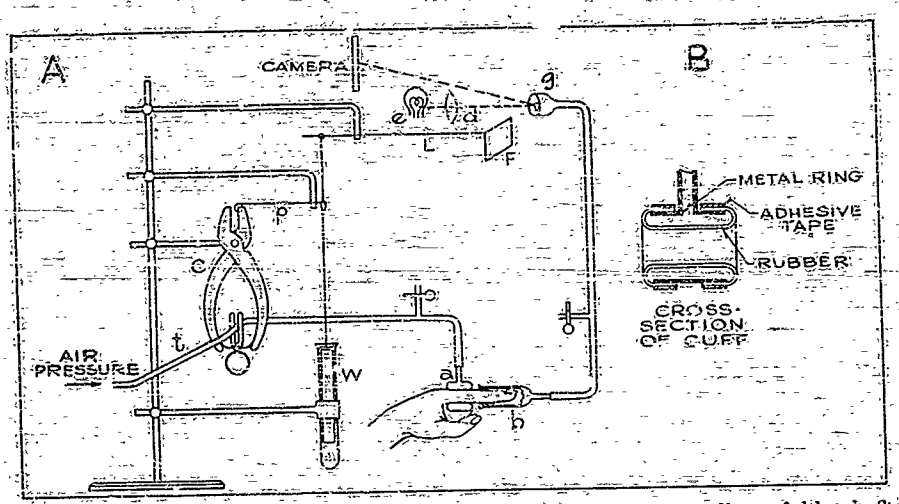

FIG. 1. A. DIAGRAM OF THE APPARATUS used for automatic recording of blood flow through the finger by the plethysmography method. B. CROSS SECTION DIAGRAM of the pneumatic cuff; *a*. See text for further details.

every 15 seconds or oftener if desired. The apparatus was usually so adjusted that the length of the upstrokes measured the amount of filling which occurred during the first few seconds after venous occlusion. The deflections were recorded on a slow drum (0.9 mm. per sec.). The volume flow per second was read from the length of the upstroke (by a calibration table) after deducting the value of the cuff artifact.

During these measurements the subject was seated with the arm resting comfortably on a table at or slightly below heart level. Pressure was applied to the lungs by a pressure helmet closed at the neck by a sponge rubber collar taken from a Drinker respirator. A steady flow of air through the helmet avoided accumulation of CO_2. To increase the pressure the outflow from the helmet was made to pass through a spring-loaded valve set usually for a pressure of 30 cm. H_2O. The pressure helmet was worn throughout the experiment.

Ordinarily 10 or 12 measurements were taken while the subject was breathing under normal pressure, a similar series under positive pulmonary pressure of 30 cm. H_2O, and a final series during recovery at normal pressure. In some experiments, rate of flow was also measured with the subject breathing under normal pressure but wearing an arm cuff inflated to 25 mm. Hg, in order to compare the effects of raised venous pressure *per se* with the effects of positive pressure breathing. In these cases, the measurements with arm cuff inflated followed immediately after the initial period of normal breathing. Each series required about 2 minutes, so that only 6 to 10 minutes were consumed by an entire experiment unless it was desired to test the effects of longer exposures to positive intrapulmonary pressure.

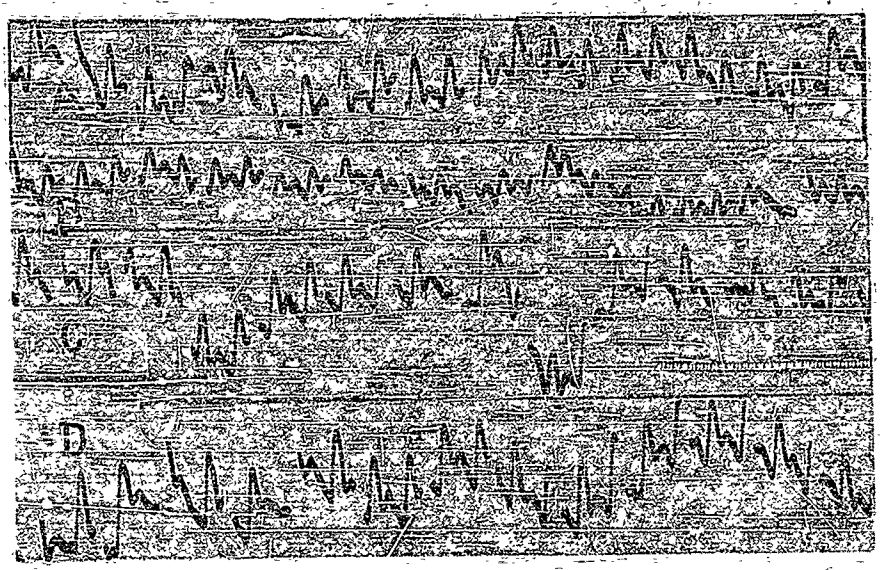

FIG. 2. EFFECT OF PRESSURE BREATHING ON THE FINGER PULSE. *A*. Normal pulmonary pressure. *B*. Beginning of pressure breathing at 30 cm. H_2O. *C*. After 5 minutes of pressure breathing. *D*. Immediately after return to normal pulmonary pressure. Time gaps in record are at 1-second intervals.

Some of the best results were obtained when the arm was immersed to the elbow in a water bath at 34–35° C. This ensures a considerable and reasonably constant degree of vasodilatation. However, most of our measurements were made at room temperature. Fluctuations in degree of vasodilatation, due to factors other than those which were being studied, probably account for a considerable proportion of the scatter found in our results.

RESULTS. *a) Volume pulse.* As may be seen from the typical record presented in figure 2, volume pulse is decreased for a few seconds immediately after positive pressure breathing begins, but usually rises again to a value near the normal level on continued exposure. Upon returning to normal air pressure, the pulse rises above the original normal value for a short time, and then sub-

sides gradually. Individuals vary considerably in the degree of response and in its time relations, and the same individual may give diverse results on different occasions.

b) Rate of blood flow. A typical record obtained with the apparatus shown in figure 1 is shown in figure 3. Each test consists of a short base-line record followed by a sharp upstroke. Between these tests the record is blank while the apparatus was being reset. The exact magnitude of the upstroke varies to some extent according to the particular phase of the cardiac or respiratory cycle. The record shows no essential change when a cuff pressure of 25 mm. Hg was applied to the experimental arm but a sharp and persistent decrease when a pressure of 30 cm. H_2O was applied to the lungs.

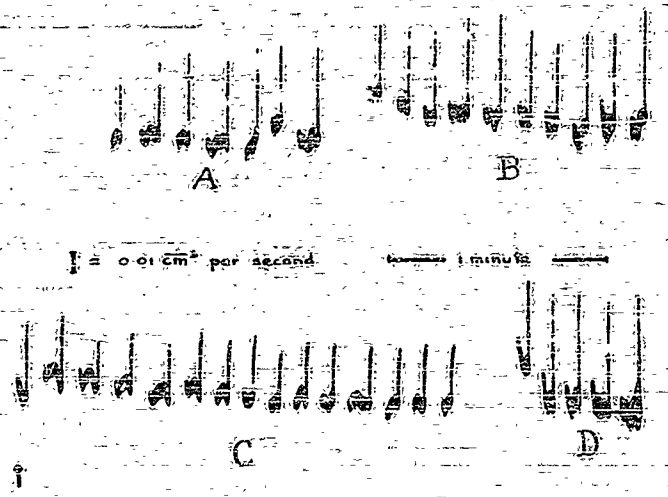

FIG. 3. RATE OF BLOOD FLOW THROUGH FINGER DURING PRESSURE BREATHING. The length of the upstroke represents the rate of flow. *A*. Normal. *B*. Inflation of pneumatic cuff on arm to 25 mm. Hg. *C*. Pressure breathing at 30 cm. H_2O beginning at arrow. *D*. Immediately after return to normal pulmonary pressure.

The results of 18 experiments are shown in table 1. For the sake of simplicity the data are presented in percentages of the normal at the beginning of each experiment. The results can be seen from the averages at the end of the table. Positive pressure breathing decreased the blood flow to 73% of normal with a standard deviation of ±17%. Immediately after the return of pressure to normal the blood flow rises to a mean value of 120% of normal with a standard deviation of ±26%. The pressure cuff at 25 mm. Hg or 34 cm. H_2O (used in the latter half of the table) decreased the blood flow to only 88% of normal or only half as much as positive pulmonary pressure, in spite of the fact that the cuff increased the venous pressure about twice as much as would be expected from the amount of PPB which was used (i.e. 15 cm. H_2O or about half the pulmonary pressure). It seems evident from this that the decrease in blood flow due to PPB was chiefly due to a vasoconstriction and only to a small extent due to an increased venous pressure.

As indicated in table 1, two experiments were tried in which the PPB was continued for 5 to 7 minutes during which time the blood flow showed no signs of returning to its normal value. With lower pulmonary pressures or in a different individual some recovery might occur as suggested by the recovery of the

TABLE 1. *Comparison of peripheral flow under locally increased venous pressure and during positive pressure breathing (PPB)*

SUBJECT	DATE	PERIPHERAL BLOOD FLOW, IN PER CENT OF NORMAL BEFORE PPB		
		Pulmonary pressure normal with arm cuff 25 mm. Hg	Pulmonary pressure +30 cm. H_2O	Pulmonary pressure normal (recovery)
W. O. F.	11-13-42		82	123
	11-13-42		58	93
	11-13-42		94	125
	11-18-42		51	74
	11-23-42		54	123
W. D.	11-18-42		83	112
L. E. C.	11-17-42		79	114
	11-18-42		96	123
	12- 3-42		86 (74)[1]	106
	12- 3-42		73 (70)[1]	119
W. O. F.	11-22-42	90[2]	71	116
H. R.	11-27-42	64	50	101
L. E. C.	11-25-42	130	64[4]	168
	11-27-42	59	61[4]	129
	11-27-42	87[3]	56[4]	118
	11-30-42	91	57	82
	12- 1-42	81	94	163
	12- 1-42	105	100	170
Mean		88	73	120
Standard deviation		±23	±17	±26
N		8	18	18

[1] Later readings after 5–7 minutes of pressure breathing
[2] Arm cuff inflated to 20 mm. Hg.
[3] Arm cuff inflated to 30 mm. Hg.
[4] Pulmonary pressure +35 cm. H_2O.

volume pulse shown in figure 2. Occasional records have shown some recovery even during the first two minutes of PPB but on the whole this is not typical of our series.

DISCUSSION. The occurrence of a vasoconstriction in the fingers during pressure breathing is not surprising since a similar reflex is known to result from a single deep inspiration (2, 3). It might be supposed that this results merely

from the expansion of the chest which is common to both PB and inspiration but vasoconstriction has been found to occur in so many respiratory acts (4) that this conclusion is not yet warranted. A diminution in the pulse volume with pressure breathing was observed by Barach *et al.* (5), by palpation, and a transient skin cooling was reported by Bateman and Sheard (6). Further data from our laboratory likewise demonstrate a clear vasoconstriction by a boot plethysmograph method (8) and by skin cooling (to be published). Other related observations are recorded in a recent survey of the subject of pressure breathing (7).

SUMMARY

A method is described by which the rate of blood flow through the finger can be recorded optically every 15 seconds. It is shown that positive pressure breathing results in a decrease in the volume of the finger pulse and a decrease in the rate of blood flow.

We wish to express our indebtedness to our colleagues Drs. Hermann Rahn and Arthur B. Otis who were closely associated with us in this work.

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CAUSES OF SKIN COOLING IN PRESSURE BREATHING, DEEP INSPIRATION AND DEEP EXPIRATION

VINCENT DE LALLA, JR.

Transient peripheral vasoconstriction has been observed incident to positive pressure breathing (P.P.B.) (1, 2). It was considered possible that this vasoconstriction originated from stretch receptors located in the lungs or chest wall. Therefore it seemed of interest to discover what effect a pneumatic vest would have during P.P.B. since the vest largely prevented abnormal expansion of the chest. The results are also of interest from the more general point of view of the vasoconstrictor reflexes which originate from negative pressure breathing, deep inspiration and deep expiration.

METHODS

Skin temperature was measured with very light copper-constantan junctions which were attached to the skin with Scotch tape or collodion. In some experiments a separate thermocouple was attached to each finger and these were read in rotation each in series with its own cold junction in ice water. For the recording experiments several such pairs of junctions were used in series and the potential of the whole series was recorded on an optical kymograph with an HS Leeds Northrup galvanometer. This arrangement gave 4 to 5 cm. deflection for one degree Centigrade. Efforts were made to measure skin temperature of the toes simultaneously, but it was found that the temperature of the fingers was far more sensitive to vasomotor influences of this type. Various types of applicators for holding a series of thermojunctions against the skin were also tried but they proved unsatisfactory either because of their large heat capacity or because the pressure which they exerted occluded the vessels which were under observation. The method which we adopted gave no pressure against the skin, minimal heat capacity and a minimal protection against the temperature changes in the environment.

In addition to the skin temperature we used a finger plethysmograph similar to that described by Fenn and Chadwick (1). This included a pneumatic cuff around the base of the finger so that rates of blood flow could also be recorded optically. A boot plethysmograph was also used for some purposes similar to that described by Fenn, Otis, Rahn and Chadwick (2).

Negative pulmonary pressures down to −20 cm of water were obtained by connecting a suction pump to a large tank and allowing the subject to inspire through a pressure face mask (A-13 U. S. Army Air Force) connected to the tank.

Expired air was eliminated through a Linde air loaded valve in the mask. Negative pressure-breathing was administered continuously for approximately 10 minutes until a stable skin temperature was reached.

Positive pressures of 20 cm. of H_2O were obtained by use of a Pioneer pressure demand valve on a high pressure (40 p.s.i.) air line, connected to an A-13 face mask worn by the subject, the expiratory port being in the mask as described above.

P.P.B. was administered continuously during two periods of approximately 10 minutes each (until a constant skin temperature was established) with an intervening rest period of 10 minutes. An inflated pneumatic vest was worn during one of the two periods of P.P.B.

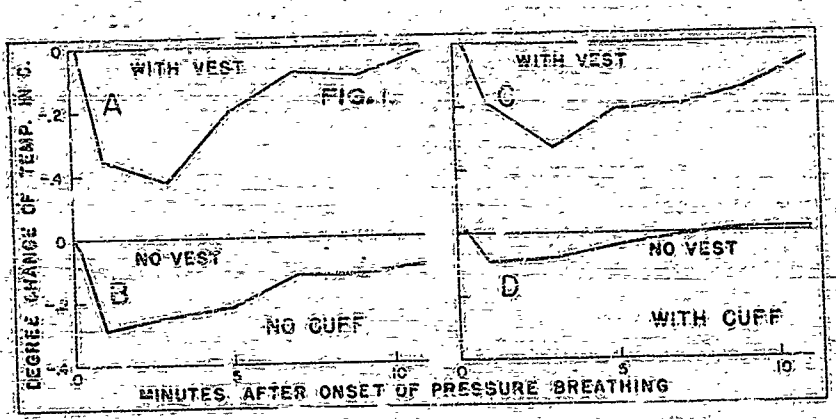
The pneumatic vest used for these experiments was supplied by the U. S. Navy and was connected into the inspired air line in parallel with the subject so that the vest was always inflated to the same pressure as the lungs. It served, therefore, to prevent any abnormal expansion of the chest during P.P.B. but did not interfere with normal breathing. On some of these same subjects an arm cuff was applied around the middle third of the upper arm on the same side as the thermocouples. This was inflated to 70 mm. Hg 15 minutes prior to onset of P.P.B. and kept inflated at that level for the remainder of the run. At this pressure the cuff prevents venous pressure changes which originate in the thorax from being transmitted back through venous channels to the hand, and presumably maintains the distal venous pressure at a constant level. In five subjects the vest was kept inflated to the same pressure that obtained in the mask during the first period of pressure breathing, and in six subjects it was inflated during the second period of pressure breathing. This compensated for any errors introduced by fatigue when comparing P.P.B. effects without vest to P.P.B. effects with vest.

Young healthy males were used in all experiments. In all cases the subjects were allowed to rest for at least 20 minutes prior to the experiments so that skin temperature fluctuations could approach an equilibrium value. It is worth noting that in the case of deep expiration the subjects were instructed to prevent a deep inspiration from following their forced expiration, and the reverse with deep inspirations.

RESULTS

Positive pressure breathing. A summary of the effects of P.P.B. on skin temperature is shown in figure 1. In all of 11 subjects tested P.P.B. produced rapid cooling of the fingers, reaching an average maximum intensity of −0.3°C. below normal in an average time of one minute after onset of P.P.B. Thereafter the skin temperature gradually returned toward normal until by the seventh minute (average) a new base line slightly cooler than normal was established (fig. 1B). This confirms the report of Bateman and Sheard (3). The range of individual responses can be determined from figures 2A and 2C.

In general the use of an inflated vest increased the magnitude of skin cooling which resulted (compare figs. 1A and 1B). This was true in all five subjects



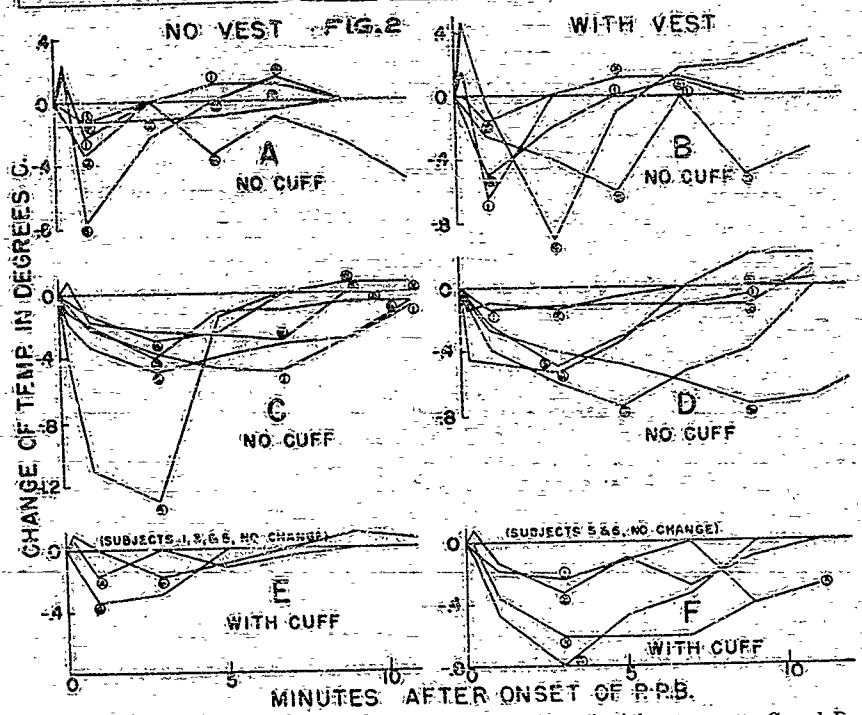


FIG. 1. EFFECT OF P.P.B. ON SKIN TEMPERATURE, with and without a vest: *C* and *D* with and *A* and *B* without a cuff. The graphs represent the average of all the results in each category. P.P.B. started at zero minutes and continued throughout in each case. The temperature scale represents deviation from the base line.

FIG. 2. EFFECT OF CONTINUOUS P.P.B. ON SKIN TEMPERATURE. Three series of experiments, each on five or six subjects, are represented by *a*) groups *A* and *B*, *b*) groups *C* and *D*, *c*) groups *E* and *F*. Groups *B*, *D* and *F* wore an inflated vest; groups *A*, *C* and *E* did not wear a vest. Groups *B*, *C* and *F* preceded groups *A*, *D* and *E*, respectively, with a 10-minute intervening rest period. The numbers on the graphs refer to subjects. Subject No. 1 in *A* is the same as subject No. 1 in *B* but not necessarily the same as subject No. 1 in *C* or *E*. Figures *C* and *D* are similarly related, as are *E* and *F*. P.P.B. started in all cases at zero minutes.

in which the experiment was so run that the period with the vest was tried before the period without the vest (compare figs. 2A and 2B). When the order was reversed (i.e., the vest inflated during the second period of P.P.B.), the vest enhanced the skin cooling in three out of six subjects, indicating perhaps, a fatigue effect (compare figs. 2C and 2D).

A pneumatic cuff was applied to the upper arm above the thermocouples in six cases. In three out of these six cases, no change with P.P.B. was demonstrable; in the remaining three there was a slight cooling effect (fig. 2E). Figure 1D shows the average curve. In these same six subjects, when the vest was inflated together with the arm cuff, the skin cooling was magnified materially in four cases. Compare figures 1C with 1D and 2E with 2F. In eight of the 34 trials of P.P.B., an initial warming effect was noted during the first 15 seconds (see fig. 2, 3A and 3B).

Typical galvanometer records of skin cooling with pressure breathing are shown in figures 3A and 3B, with and without the vest, respectively. The existence of vasoconstriction in the finger was confirmed by records taken with the finger plethysmograph, examples of which are shown in figures 3D and 3E.

In the experiments from which the average curves of figure 1 were taken, there is probably not enough data to establish the relative positions of all the curves with certainty. Since, however, in all cases without a cuff there was cooling of the skin, the presence of a vasoconstriction seems established beyond any doubt. Furthermore, it seems certain that the addition of a pneumatic vest to keep the chest movements in the normal range does not eliminate but seems to enhance the magnitude of the reflex vasoconstriction. This seems to prove clearly that the reflex is not initiated by an expansion of the chest.

Our work with P.P.B. in four subjects confirmed the diminution of foot volume with P.P.B. (during partial occlusion by a leg cuff) reported by Fenn and coworkers (2); in four other subjects a diminution of finger volume was also demonstrated in all cases when a finger cuff had been previously inflated to 60 mm. Hg (see fig. 3D). One subject in each group wore an inflated vest without apparent effect upon the response (see fig. 3E).

Negative pressure-breathing. In five subjects skin cooling varied from −0.1°C. to −0.6°C. below normal and lasted from one to four minutes. In two of these subjects finger volumes were recorded on the same film and a simultaneous diminution of finger volume was shown to occur. A record of such an experiment is shown in figure 3C. It is significant and perhaps surprising that the effect of negative pressure is the same rather than the opposite of the effect of positive pressure.

Deep inspiration. Early in these experiments the vasoconstrictor effect of a deep inspiration and later of a deep expiration was noticed. Repeated records were taken by the various methods described above in the hope of learning more about the nature of these respiratory vasomotor reflexes. The results of a deep inspiration may be summarized as follows.

In five subjects skin cooling varied from 0.15°C. to 0.57°C. below normal and lasted from 1.5 to 5 minutes. A typical record is shown in figure 4A. In six

other subjects, finger volume diminished in all cases, the diminution lasting from 0.5 to 2.5 minutes. In four subjects, rates of finger blood flow (cc/sec.) were measured by the method of Fenn and Chadwick (1) and they diminished 30 to 90 per cent, returning to normal within 1.5 minutes. A record of such an

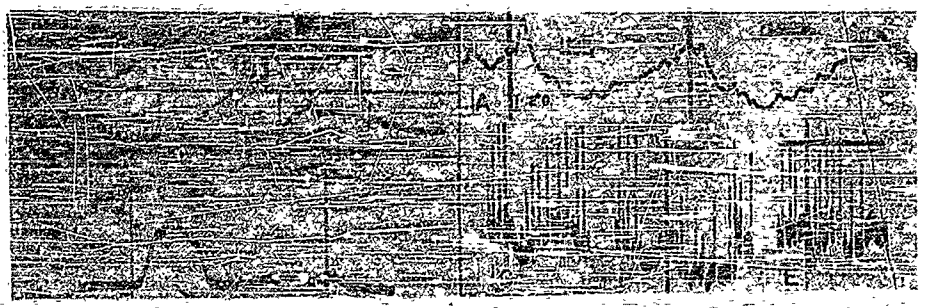


FIG. 3. FIG. 4.

FIG. 3. *3A*. SKIN TEMPERATURE RECORD OF P.P.B. with vest inflated showing cooling (downward deflection). P.P.B. turned on at vertical line. *3B*. Skin temperature record of P.P.B. without vest. P.P.B. started at vertical line. Same subject as in 3A; same time and temperature scale as in 3A. *3C*. Simultaneous skin temperature (dotted line) and finger volume recorded during negative pressure breathing, started at first vertical line and stopped at second vertical line. Cooling is represented by the downward deflection of the dotted line, and diminished finger volume is represented by the upward deflection of the solid line. *3D*. Finger volume record during P.P.B. without vest and with inflated finger cuff, starting at first vertical line and stopping at second, showing diminution of finger volume (upward deflection). In 3C and 3D, time scale is one half that of 3A. *3E*. Simultaneous skin temperature (dotted line) and finger volume curves (different fingers of same hand) recorded on same subject as 3D during P.P.B. with vest inflated. Finger cuff inflated only on finger producing the lower record. Note simultaneous cooling of skin (downward deflection of top line) and diminution of finger volume (upward deflection of bottom). Time scale as in 3A. Interruptions in records in *A*, *C* and *E* at 13.5 sec.

FIG. 4. *4A*. SKIN TEMPERATURE RECORD SHOWING COOLING (downward deflection) following a single deep inspiration at solid vertical line. *4B*. Continuous with 4A, showing skin cooling following a single deep expiration at solid vertical line. *4C*. Diminished rates of arterial blood flow in the finger and diminished finger volume following a single deep inspiration at solid vertical line. Rates of flow indicated by height of spikes above base line. Note that first attempt to record rate of flow after the deep inspiration indicates zero flow. The wide base line indicates finger volume diminution (downward deflection) occurring simultaneously with the diminished rate of blood flow. 4D and 4E are records similar to 4C but for a single deep expiration taken at the solid vertical line in each case. Again note the absent or nearly absent spikes directly following deep expiration. The time scale is constant for all records as indicated in *A*. Time intervals of 13.5 sec. indicated in *E*.

experiment is shown in figure 4C. Each upstroke starts at the moment when a pneumatic cuff around the base of the finger is inflated and terminates after a given interval of time a few seconds later. The height of the upstroke is then a direct measure of the rate of flow. The black line extending both above and below the base line marks the time of a single rapid deep inspiration. Following this the first inflation of the cuff (just before the first gap in the record) gave no

filling at all. The second inflation gave a very small flow and successive inflations at intervals of 10 to 20 seconds revealed blood flow gradually returning to normal. There is also a simultaneous drop in base line, representing a diminution of finger volume. This tracing is an excellent demonstration of the dramatic vasoconstrictive effects of a deep breath. The drop in blood flow to almost zero confirms the statement of Mulinos and Shriman (11) that blood flow in the finger nail capillaries stops immediately following a deep inspiration.

A cuff was inflated to 60 mm. Hg around the experimental arm prior to the deep inspiration and maintained during the run in four cases. Skin temperature measured in one of these revealed skin cooling of 0.5°C. after a deep inspiration with recovery in five minutes. In the other three subjects finger volumes diminished with recovery occurring in 0.5 to 1 minute.

Deep expiration. In five subjects skin cooling after a deep expiration varied from 0.1°C. to 0.6°C. below normal and lasted from one to three minutes (see fig. 4B). In six other subjects finger volume diminished in all cases, the diminution lasting from 0.5 to 2.5 minutes. Measurements of the rate of blood flow in three subjects showed a diminution of 80–90 per cent and a return to the normal value within 0.5 to 1.5 minutes.

In two subjects foot volumes were measured. In one case foot volume diminished with both a deep inspiration and a deep expiration. In the second subject records of finger and foot volumes, recorded photographically on the same film, indicated simultaneous diminution of finger and foot volume following both deep inspiration and expiration and simultaneous recovery within 60 seconds.

It is interesting that the effects of deep inspiration and deep expiration are so similar in their reflex vasomotor effects. This finding does not confirm the report of Bolton, Carmichael and Stürup (10), who found that expiration had no effect on the finger volume. This discrepancy may possibly be due to differences between subjects or to different techniques of carrying out the deep expiration. Our studies have not been sufficiently exhaustive to settle this matter. It might be mentioned, however, that the case is somewhat parallel to positive and negative pressure breathing, both of which had the same reflex effect on the blood vessels. The similarity in the effects of expiration and inspiration is another indication that the size of the chest per se does not determine the nature of the reflex effect which is set up.

DISCUSSION

Perhaps the most surprising aspect of the results obtained is the fact that reflex peripheral vasoconstriction occurred after both positive and negative pressure breathing, and after both deep rapid inspirations and deep rapid expirations.

Transient skin cooling incident to P.P.B. was first noted by Bateman and Sheard (3). That this skin cooling is due to a reflex peripheral vasoconstriction seems reasonably well established by the demonstration of coincident transient diminution of pulse volume and of rate of peripheral blood flow (1, 2). The cause for the initial skin-warming effect is obscure, but it seems possible that it

represents an initial rise in peripheral blood flow caused by the increased left heart output which occurs for a few seconds after the onset of P.P.B. As P.P.B. is applied the pulmonary blood pool is reduced because the increased intrapulmonary pressure not only impedes the systemic venous return but also forces blood out of the lungs. Thus the initial effect is to increase the left heart output at the same time that the right heart output is decreased. Some seconds later, however, balance is restored and the left heart output is diminished.

It might be argued that the diminished venous pressure gradient from periphery to heart which occurs with P.P.B. (4) is responsible for the skin cooling. In all probability it accounts for a portion of it, since we have demonstrated that the cooling effect of P.P.B. in the fingers is lessened by an inflated arm cuff (see fig. 1). But this cuff largely prevents transmission of pressure changes from thorax to finger, so it is readily seen that there is at least one other factor.

Cardiac output studies (6, 7) have revealed a slight decrease in both stroke and minute volumes in humans during P.P.B. Here again, it might be said that the reduced peripheral blood flow secondary to diminished cardiac output could explain the observed skin-cooling effect. However, arterial blood pressure in the arm (relative to the atmosphere) is increased by P.P.B. (5). Therefore, a diminished cardiac output alone could not reduce the blood flow in the finger unless accompanied by a peripheral vasoconstriction. Furthermore, the reduced cardiac output endures throughout P.P.B., whereas the skin-cooling effect is transient. If a marked transient diminution is ascribed to the left cardiac output as a result of the diminished venous return to the right heart, it must be noted that the hemodynamics probably readjust within a fraction of a minute to the stable enduring cardiac output which has been reported. In contrast the peak skin-cooling effect occurs within 2–3 minutes and may last 9–11 minutes.

The experiments reported in this paper offer further evidence for this vasomotor reflex, but they show in addition that the reflex is not initiated by the inflation of the chest which occurs in P.P.B. because it is not diminished when an inflated vest is worn to prevent abnormal chest expansion. (The use of a vest increased the skin cooling effect of P.P.B. in 12 of the total of 17 experiments; see fig. 2.) Furthermore, it occurs in negative pressure breathing as well as in positive pressure breathing. The reflex seems to involve the same mechanism which operates during deep inspiration and deep expiration, both of which are shown to be accompanied by a peripheral vasoconstriction.

In 1895 Binet and Sollier first observed a diminution of hand and cerebral volume following a deep inspiration (8). Uhlenbruck in 1924, as a result of his observations of arm and foot volumes, stated that all voluntary changes of respiration such as coughing, laughing, sighing, etc. produced peripheral vasoconstriction (9). Since then numerous observers have noted this phenomenon (10, 11, 15, 16). The work of Bolton *et al.* (10) and Mulinos and Shulman (11) seems to prove that this diminution in peripheral volume following a deep inspiration is a true reflex. Bolton demonstrated that it did not occur in the sympathectomized limb, and Mulinos and Shulman showed that it occurred distal to an arm cuff inflated to complete occlusion. Our own work demon-

strates that reduced finger volume and skin cooling occurs distal to a partially occluding arm cuff following not only deep inspiration but also deep expiration, indicating in both instances that the observed results are not directly due to pressure changes originating in the thorax, and transmitted through the veins.

This identical response to seemingly opposite causes is perplexing and makes interpretation difficult. However, consider the hemodynamics in each case, with regard to intrapleural pressure and its effect in venous return. It will be noted that P.P.B. and a deep expiration have the same effects in that both increase the intrapleural pressure and thereby diminish the venous return. Similarly negative pressure breathing and a deep inspiration can be related, in that both diminish the intrapleural pressure and consequently increase the venous return.

In the first case the dammed venous blood will stretch the extra thoracic veins, as demonstrated by Holt (4), Otis *et al.* (6) and Carr and Essex (17). In the second case the increased venous return must stretch the large intrathoracic caval veins and the right auricle.

In 1934 McDowall (12) demonstrated that stretching the right auricle produced peripheral vasoconstriction. In 1937 Nonidez (13) demonstrated histologically the presence of what he called stretch receptors in the intrapericardial portions of the inferior and superior vena cavae and pulmonary veins. It is therefore quite logical to assume that it is the stretching of the right auricle and the large intrathoracic veins that initiates the peripheral vasoconstriction incident to a deep inspiration and negative pressure breathing, since both of those maneuvers diminish the intrapleural pressure, thereby increasing the venous return to the heart and dilating the heart and veins.

If we postulate similar stretch receptors in the extrathoracic large veins, we might possibly explain the reflex peripheral vasoconstriction incident to a deep expiration and positive pressure breathing, since both of these raise the intrapleural pressure, thereby damming venous blood and causing the extrathoracic veins to stretch. It is in accord with this theory that the use of a vest with P.P.B., which increases the rise in intrapleural pressure (6, 14), thereby further impeding venous return and causing increased stretching of the large extra thoracic veins, likewise seems to increase the reflex skin cooling.

But this explanation appears paradoxical since it requires that as the central pressoreceptors relax, causing a relative arterial vasodilation, the peripheral pressoreceptors are stimulated, resulting in arterial vasoconstriction. However, there are certainly other instances where one reflex dominates over another; furthermore, evidence for the existence of pressoreceptors in the abdominal vena cava might be construed from the work of Erlanger and Gasser (18). When they partially occluded the inferior vena cava in dogs, thus damming blood back into the abdomen, they noted an increase in peripheral vasomotor tone as determined by rate of inflow into the femoral artery. It is possible that this vasoconstriction might have been reflexly initiated by stimulation of pressoreceptors in the abdominal vena cava.

Perhaps a simpler interpretation would be that the observed vasoconstriction

in all cases represents an irradiation from the respiratory center to the vasomotor center as a result of rather strenuous voluntary or conscious changes in normal respiration comparable possibly to an alarm reaction. This latter hypothesis, however, fails to explain the increased reflex vasoconstriction when a pneumatic vest is worn, and it ignores the demonstrated presence of pressoreceptors in right auricle and large intrathoracic veins capable of producing the vasoconstriction observed with negative P.B. and deep inspiration. A more specific hypothesis is to be preferred.

SUMMARY

1. Further evidence from skin temperature and plethysmograph measurements is presented to show that positive pressure breathing results in a peripheral vasoconstriction.

2. This reflex does not depend upon an expansion of the chest, because it occurs equally well in negative pressure breathing and equally well or perhaps even better when expansion of the chest due to positive P.B. is prevented by the wearing of a pneumatic vest by the subject.

3. A similar reflex occurs after either a single deep rapid inspiration or a single deep rapid expiration.

4. It is thought likely that the vasomotor reflex incident to a deep inspiration and negative pressure originates from pressoreceptors in right auricle and intrathoracic large veins.

The author wishes to express his sincere gratitude to Professor Wallace O. Fenn for his patient instruction and constructive criticisms, without which this work would not have been possible. It also gives pleasure to acknowledge the aid of Dr. Elmer Tuttle in the construction of the finger plethysmograph, and the many well-received advices of Dr. Hermann Rahn and Dr. Arthur B. Otis.

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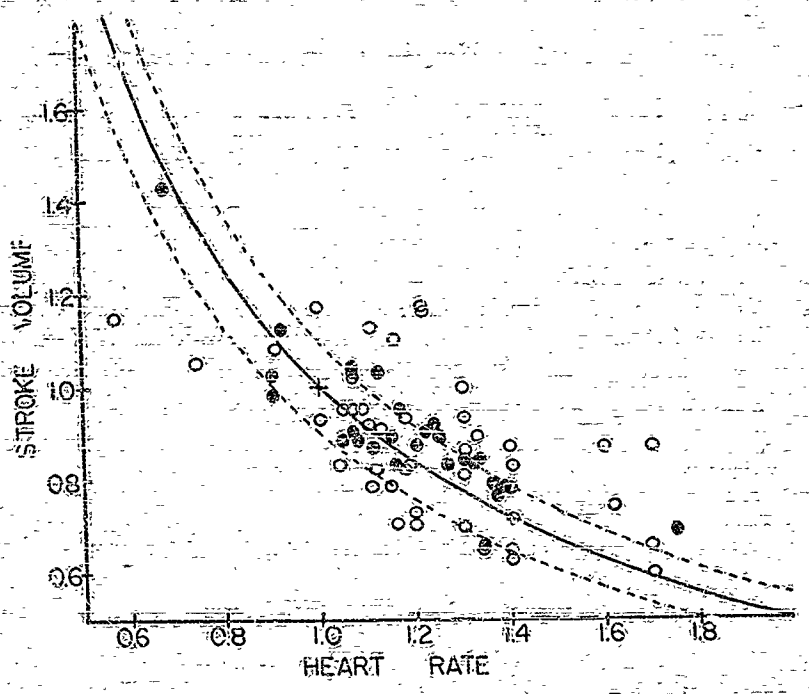

FIG. 2. THE EFFECT OF BREATHING AGAINST POSITIVE PRESSURE ON THE STROKE VOLUME, AND HEART-RATE

Each point represents a comparison between normal and experimental conditions, heart rate and stroke volume being expressed each as a fraction of the normal value taken as 1.0. The normal is therefore represented by the cross (+) at point 1.0, 1.0 on the diagram, and all the points are relative experimental values. The solid line is a rectangular hyperbola passing through the cross and indicating points where the product of heart rate and stroke volume, or the cardiac output, is constant and normal. Broken lines represent cardiac output 10 per cent above (on the right) or below (on the left) normal. Open circles = horizontal, and closed circles = vertical ballistocardiograph. Note that the points lie in general to the right of the cross (increased heart rate) but below (decreased stroke) so that they scatter more or less uniformly both above and below the solid curve. This indicates no average change in cardiac output.

deflection); A = aortic cross section in sq. cm.; C = duration in seconds of one cardiac cycle.

In most cases we made no effort to calculate the cardiac output or stroke volume in absolute units, but determined only relative magnitudes.

A typical normal record is shown in Figure 1, demonstrating that the tracings are clear and easily measured and in general similar to those published by Starr *et al.* (2).

RESULTS

(1). *Changes in intrapulmonary pressure*

In this series of experiments positive pressure was applied to the lungs either through a mouth piece for short periods or for longer periods through a helmet which covered the whole head and which was sealed around the neck with a Drinker respirator type of sponge rubber collar. The subjects breathed air of which the pressure was controlled between 25 and 30 cm. H_2O by a limit valve, and the flow was sufficient to prevent the accumulation of carbon dioxide. The mouthpiece could not be used for long periods on account of the resulting fatigue of the cheek muscles. In the sitting position we have 14 experiments on 8 different male subjects; in the supine position, 17 experiments on 14 subjects. The results may conveniently be summarized in Figure 2, in which the ordinates represent stroke volumes as a fraction of the nor-

mal stroke volume, and abscissae represent heart rates expressed as a fraction of the normal heart rate. In such a graph all points with a normal cardiac output of 1.0 should lie along a rectangular hyperbola passing through the point 1, 1, marked by a cross. The dotted lines indicate cardiac outputs 10 per cent greater or less than this normal. Values in the sitting position are indicated by solid circles and those in the supine position by open circles. It is evident from this chart that in most cases there is little change in cardiac output, although some subjects show an increase and some a decrease. However, there is a well marked tendency for the stroke volume to decrease and the heart rate to increase enough to compensate. In a few cases the heart rate decreased and the stroke volume increased. The two points showing the greatest decrease in cardiac output are on the same subject, a 19-year-old girl whose heart failed to accelerate enough to maintain the cardiac output even though the stroke volume was above normal.

The grand average of all the figures shows an increase of heart rate of 1.18 times while the stroke volume decreased to 0.89 of the normal. The product of these two gives a cardiac output 1.05 times the normal. From the same experiments average values, including both sitting and supine figures, have also been obtained at different times from 15 seconds to 10 minutes after the beginning of pressure breathing, but no consistent change with time could be discerned. The heart rapidly adjusts itself to the unusual conditions and maintains this adjustment with a fairly constant value. On the average, the cardiac output, so measured, does not differ significantly from the normal at pressures up to 30 cm. H_2O, although there are certain individuals at certain times who do show a decrease.

Higher pressures for short periods of time have been tested in two subjects who were asked to exert voluntary pressure against a mercury manometer as in the Flack test for circulatory efficiency (3) or the test outlined by Bürger (4). In these cases the stroke volume did diminish, but the heart rate increased enough to more than compensate so that in one subject at 50 mm. Hg. the cardiac output was 158 per cent of normal, while in the other at 40 mm. Hg. it was 119 per cent of normal.

For purposes of comparison, a few experiments have been carried out on subjects breathing under conditions of negative pulmonary pressures of — 30 cm. H_2O. Under these conditions also no significant change in cardiac output was found. For 12 cases for periods up to 4 minutes the average values relative to the normal were: stroke volume, 1.0, heart rate, 1.1, cardiac output 1.1.

It should be pointed out that all these experiments were carried out on untrained subjects, largely medical students. The application of positive pulmonary pressure by mouthpiece becomes quite uncomfortable in a very short time and application of pressure via a helmet is no more reassuring to the uninitiated subject. The average time at which these records were taken is less than 3 minutes and one-third of the records were taken less than a minute after applying pressure. In view of the necessary anxiety and short period for adjustment the quantitative results must be accepted with some reservations.

Consequently, another series was obtained on 6 subjects who had had previous experience with pressure breathing in connection with other experiments. Ample time was allowed for these men to adjust themselves to the positive pressure which was administered through a mouthpiece, mask or helmet, and records were taken 10 to 40 minutes later. The results are shown in Table I, all values being expressed in percentage of normal. The results were consistent in showing an increase in heart rate, decrease in stroke volume, a decrease in cardiac output and pulse pressure

TABLE I

Effect of positive pulmonary pressure of 30 cm. H_2O

Subject	Heart rate	Stroke vol.	Cardiac output	Systolic pressure	Diastolic pressure	Pulse pressure
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
RD	115	71	82	107	113	98
PB	113	76	85	108	120	84
WF	111	86	98	104	109	96
PS	115	65	75	100	110	85
AO	111	83	94			
AC*	122	65	79	106	115	91
Average	115	74	86	105	113	91

* These results are averages of many experiments on a single subject with 30 cm. H_2O applied in different ways as follows: 7 experiments using an aviation mask, 6 experiments using a helmet, 4 experiments with a mask and a pneumatic vest (Mae West) for the application of counter pressure to the chest, 12 experiments with a helmet and vest and 1 experiment using a mouth piece.

All quantities in percentage of normal.

TABLE II

Effect of artificially forced respiration (Pneumolator) on the cardiac output.

Subject	Heart rate	Stroke volume	Cardiac output
	per cent	*per cent*	*per cent*
RD	89	102	90
HR	112	77	86
AH	93	102	95
AO	78	93	72
Av. of 6*	96	90	85
Grand Av.	95	91	85

*Individual data on these 6 subjects are presented in Table III. The peak pressure on the pneumolator was 20 to 25 cm. H_2O, frequency 7 to 9 per minute.
All values in percentage of normal.

but an increase in both systolic and diastolic pressure.

The last line in Table I summarizes a number of experiments on one subject (A.C.) who breathed against 30 cm. H_2O positive pressure applied with a mask or with a helmet, and with and without counter-pressure from a pneumatic vest. Only average figures of all the experiments are given because the variations in the method of application of the pressure made no difference. All the experiments were similar qualitatively and showed on the average a 14 per cent decrease of the cardiac output. This figure approaches the results of Richards (5) obtained by the direct Fick method on 4 patients breathing 27 cm. H_2O.

(2) *Effects of intermittently elevated pressure with the pneumolator*

Some further experiments were tried with intermittent pressure breathing or artificially forced respiration. For this purpose we used an apparatus built by the General Electric X-ray Corporation called a pneumolator. This instrument supplies oxygen or air to a mask which is inflated along with the lungs until a critical pressure is reached. At this point the inflow of oxygen automatically stops and an expiratory port is opened so that the pressure can slowly fall to zero at a rate which can be controlled by a variable gate. The value of the peak pressure can be controlled for each experiment. As soon as the pressure reaches zero the expiratory port is closed and inflow starts again. The mean pressure in the lungs during a cycle is about 40 per cent of the peak pressure, so this is a form of pressure breathing. Since, however, the pressure is higher in inspiration than in expiration, the process tends to increase the depth of respiration and lowers the alveolar carbon dioxide tension. Breathing through this apparatus is easier than against a continuous pressure, but it is insidious because it is likely to lead to acapnia.

The results obtained with this type of breathing are shown in Table II. The average stroke volume is 91 per cent of normal with a mean pulmonary pressure of 8 to 10 cm. H_2O. With continuous pressure breathing the stroke volume was decreased to 74 per cent of normal with a mean pulmonary pressure of 30 cm. H_2O. It may be concluded, therefore, that the stroke volume is decreased in both cases in proportion to the mean pressure.

The data of Table II (and Table III) show that 6 out of 10 subjects breathing with the pneumolator had decreased heart rates, the average being 95 per cent of normal. This result contrasts sharply with the figures in Table I where all the subjects uniformly showed increased rates of 11 to 22 per cent over the normal. Largely due to this difference in the reflex response of the heart, the use of the pneumolator results uniformly in a decreased cardiac output averaging 85 per cent of normal.

The reason for the difference in heart rate with the two kinds of pressure breathing is not obvious, but it might possibly be attributed to the greater muscular effort involved when the pressure continues during the expiratory phase.

Brief mention should be made of some other experiments which were undertaken with the idea that the effects of pressure breathing might be artefacts due merely to the change in the degree of inflation of the chest. With a larger chest it was thought that the impacts from the heart might be less well transmitted to the body as a whole. In these experiments the subject held his breath with the glottis open at different degrees of inspiration and expiration while records were taken on the ballistocardiograph. The results showed in general a decreased heart rate at the higher degrees of inspiration in agreement with the findings of Lewis, Lewis, and Hall (6), and *vice versa* for expiration, but no significant change in the stroke volume. It is perhaps significant that the stroke

TABLE III

Effect on cardiac output of pneumolator (Pneu) and voluntary hyperventilation (VHV) at the same alveolar pCO_2

Subject	Heart rate			Stroke volume		Cardiac output		Alveolar pCO_2		
	Normal	Pneu	VHV	Pneu	VHV	Pneu	VHV	Normal	Pneu	VHV
	beats per min.	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*mm. Hg.*	*mm. Hg.*	*mm. Hg.*
M.E.	73	111	114	89	87	99	99	40.6	28.2	23.4
M.H.	67	84	93	106	107	88	99	38.7	25.0	25.1
M.B.	62	110	108	93	96	103	105	38.2	27.4	22.8
J.H. (a)	64	98	108	76	86	74	92	46.3	25.7	
(b)		100		74		73			24.9	
H.R. (a)	78	97	100	83	93	81	93	42.9	28.7	30.0
(b)		90		96		85			28.5	
B	72	88	81	98	115	84	92	36.5	32.7	29.8
		89		93		82			34.0	
Average	69	96	101	90	97	85	97	40.6	28.4	26.2

The peak pulmonary pressure on the pneumolator was 20 to 25 cm. H_2O. All values in percentage of normal unless otherwise indicated.

volume did not increase in the inflated position in spite of the decreased heart rate. The changes in the heart rate indicate some reflex cardiac effects resulting from different degrees of inflation. This does not help to explain the effects of continuous and intermittent pressure on the heart rate, because the mean lung volume was greater with the former where the heart rate was highest.

(3) Effect of decreased alveolar carbon dioxide tension

It has been shown that for the same mean pulmonary pressure the cardiac output is more diminished by intermittent than by continuous pressure breathing. This suggests the possibility that the diminished alveolar carbon dioxide tension which accompanies the use of the pneumolator may be responsible for this difference. In order to investigate this hypothesis one of us (M.B.) carried out a series of ballistocardiographic determinations on 6 different subjects in which the effects of voluntary hyperventiliation were compared to the effects of breathing on the pneumolator.

These experiments involved three periods: (*1*) 10 minutes reclining in the supine position on the ballistocardiograph breathing air normally through an A-13 mask; (*2*) 10 minutes breathing air through the pneumolator with a peak pressure of 20 to 25 cm. H_2O; (*3*) 10 minutes of voluntary hyperventilation. At the close of each period a record was taken on the ballistocardiograph followed by an alveolar air sample taken from a side tube in the mask after a forcible expiration (beginning at the end of expiration).

The results of these measurements are shown in Table III. They indicate that the cardiac output was decreased to 85 per cent of normal by the pneumolator but to only 97 per cent of normal by voluntary hyperventilation. The fall in the alveolar carbon dioxide tension was approximately the same in both cases. Similar results were obtained by Drs. Kety, Schmidt, and Starr, University of Pennsylvania (Personal Communication). The experiments with the pneumolator confirm those reported in Table II. In a second series of experiments air was delivered to the mask through a gas meter which stood in view of the subject. Every 5 seconds the subject inhaled and continued until the pointer had reached a certain point on the dial. In this way the volume of the ventilation could easily be controlled either at 12 or 18 liters per minute. The experiment consisted then of a 10-minute normal period with the mask but without the gas meter, then two 6-minute periods with the gas meter at each of the two increased tidal volumes. Records and alveolar air samples were taken near the end of each period. Three

experiments were tried on each of 5 subjects. In order to avoid disturbance of the ballistocardiographic record by the mechanical oscillations due to the increased effort of breathing, the subject was instructed to breathe normally while the record was being taken. All records were taken within 30 seconds after the cessation of hyperventilation so that it can be fairly assumed that any effects of lowered alveolar carbon dioxide tension would still be in operation.

The results of these experiments are summarized in Table IV. All the changes are very small

TABLE IV

Effects of voluntary hyperventilation of different degrees on cardiac output. Averages of 3 experiments on each of 5 subjects

Ventilation	Heart rate	Stroke volume	Cardiac output	Alveolar pCO_2
liters per min.	*per cent*	*per cent*	*per cent*	*mm. Hg*
Normal	100	100	100	44.1
12	103	96	99	34.0
18	103	92	95	24.0

but there is a well marked tendency toward a decreased cardiac output (95 per cent) and a decreased stroke volume (92 per cent) which was not balanced by an increase in heart rate (103 per cent) at the higher rate of ventilation. Intermediate values were obtained at the 12 liter per minute rate. The alveolar CO_2 tension at the higher rate was decreased to 24 mm. Hg which is comparable to the decrease observed in Table III, and the decrease in cardiac output is of the same order of magnitude. The uniformity of the 15 experiments was shown by the fact that at 18 liters per minute 11 experiments showed a decrease in cardiac output, 13 showed a decrease in stroke volume and 13 showed an increase in heart rate or no change. The 5 per cent decrease in cardiac output was statistically significant because the probable error of the mean was only ± 1.1 (Table IV).

In considering the significance of these results it might be pointed out that increased ventilation requires increased oxygen consumption. Assuming that the cardiac output is increased in proportion to the oxygen consumption, it is possible to predict on the basis of figures for the oxygen consumption in overventilation given by Liljestrand (7), that the cardiac output will be increased 3 per cent at 12 liters per minute and 7 per cent at 18 liters per minute. From these figures it might be argued that if the same ventilation could have been produced passively, so as to avoid the increased cardiac output required for this increased metabolism, the cardiac output would have been only 99 − 3 = 96 per cent at 12 liters per minute, and 95 − 7 = 88 per cent of normal at 18 liters per minute. Such figures actually were closely paralleled by those obtained with the pneumolator where the ventilation was passive although the pressure was elevated.

These results appear to indicate that there is a small but distinct decrease in cardiac output due to diminished alveolar pCO_2 but the situation is of course very complicated and the result might be attributed equally well to mechanical effects of the altered respiration. This result also does not permit the conclusion that the decrease in cardiac output observed with the pneumolator is due to the hypocapnia which is produced, because the high pulmonary pressure provides an equally good explanation. In addition, it might be mentioned that Groliman (8) using the acetylene method for cardiac output found an increase with forced ventilation, even when a fall of alveolar pCO_2 was prevented by the inspiration of suitable CO_2 mixtures. The reason for this discrepancy is not clear.

(4) Experiments with increased dead space

To complete this study some further measurements were made of the effects of increased alveolar carbon dioxide tensions obtained by increasing the dead space. The subject breathed air through a mask and 3-way cock. The two free ends of the cock were connected to open tubes containing 210 and 760 ml. respectively. By turning the cock the subject could be made to breathe in and out through either one of these tubes. Normal records were taken without the mask. Each period was continued for 15 minutes before the record was taken. This experiment was tried on each of 5 subjects. The results were variable and inconsistent. On the average, the addition of either of the two dead spaces increased the cardiac output 2 per cent over the normal value, but this difference was certainly not significant. Other experiments have shown that the alveolar pCO_2 was increased in such experiments not more than 0.5 mm. Hg and 5 mm. Hg by the 210 and 760 ml. dead spaces respectively.

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This experiment indicates that an increase of alveolar CO_2 does not increase the cardiac output, and this is consistent with the conclusions reached by Groilman (8) on the basis of the acetylene method. Indeed, if allowance is made for the increased metabolic rate which must have accompanied the increased breathing needed for these dead spaces (about 18 liters per minute with 760 ml.) the effect of the alveolar change by itself might well have been a decrease in the cardiac output.

(5) *Effects of oxygen inhalation*

Before considering the ballistocardiographic data, mention should be made of a series of experiments in which the minute volume of the ventilation was measured in three successive periods on air, then pure oxygen, and finally on air. Our purpose was to investigate some of the rather large increases of ventilation produced by oxygen breathing which had been reported, averaging 20 per cent according to Edelmann, Whitehorn, and Hitchcock (9) and 13.4 per cent according to Shock and Soley (10). All our subjects came early in the morning without breakfast and reclined for 30 minutes on a bed before the experiment began. Air or oxygen was inhaled from a spirometer through a mouth piece and valves. Each period lasted for 30 minutes and was followed by a 10-minute rest period. Ventilation was determined from the spirometer which had a capacity of 2 liters per cm. with a total of about 100 liters. In some of the experiments it was the expired air which was collected in a spirometer and measured. Results were corrected to body temperature, pressure and saturation (BTPS). Table V gives the results of 16 experiments on 6 different subjects. In the last two columns the ventilation on oxygen is expressed in percentage of the two control ventilations on air. On the average it is seen that oxygen increases the ventilation 5 ± 1.2 per cent compared to the first control, and 6 ± 0.89 per cent compared to the second control period. The standard deviations of the mean indicate a very high degree of statistical validity. It is concluded that oxygen increases the minute volume of the ventilation only 5 or 6 per cent, few if any of our figures being as high as those reported previously.

In 10 of the experiments (5 subjects) listed in Table V simultaneous measurements were made

TABLE V

The volume of the ventilation in liters per minute breathing oxygen and air

Subject	Air (1)	O_2	Air (2)	Ventilation in O_2 in percentage of air	
	liters per min.	*liters per min.*	*liters per min.*	(1)	(2)
HR	6.89	7.72	7.54	112	102
HR	7.54	8.35	7.50	109	111
HR	6.08	6.40		105	
J.H	6.74	7.15	6.45	106	111
J.H.	6.40	6.54	6.50	102	101
H.M.	5.46	5.54	5.28	101	105
H.M.	5.48	5.76	6.11	105	94
H.M.	5.60	6.18	5.81	110	106
A.C.	6.86	7.27	7.14	106	102
A.C	8.05	7.66	7.06	95	108
A.C.	7.85	7.99	7.20	102	111
A.C.	6.29	6.83	6.77	108	101
H	6.16	7.05	6.32	114	111
H	7.09	7.50	6.67	106	112
H	6.76	7.00	7.08	104	99
J.H.	5.35	5.43	4.77	101	114
Average	6.55	6.90	6.53	105	106
St. dev.	±.85	±.87	±.79	±4.7	±3.4
St. dev. of mean.	±.21	±.22	±.20	±1.2	± .89

of the stroke volume and heart rate with the ballistocardiograph. The results are summarized in Table VI. As before, the values during the oxygen period are calculated in percentage of the two control periods. The fact that these two sets of control values agree so closely shows that no progressive change was occurring in the condition of the subject. The figures show a decrease in the cardiac output during oxygen breathing in every case, averaging 8.5 per cent with a standard deviation of the mean of 1 per cent. Since the stroke volume showed on the average no change, it must be concluded that the decrease in the heart rate was responsible for the decrease in cardiac output. These results agree with those reported by Whitehorn, Edelman, and Hitchcock (11), except that they found a slightly larger decrease in cardiac output amounting to 12 per cent and found the stroke volume decreased as well as the heart rate.

DISCUSSION

The main question relative to these experiments is whether our procedure has actually measured the cardiac output. In this respect it is satisfying to

TABLE VI

Effects of oxygen inhalation on cardiac output, heart rate and stroke volume

Subject	Compared to first control period			Compared to second control period		
	Heart rate	Stroke volume	Cardiac output	Heart rate	Stroke volume	Cardiac output
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
H.R.	83	106	88	96	97	93
H.R.	83	108	90	93	100	94
J.F.	95	101	94	95	102	96
J.H.	90	98	87	96	94	91
T.H.	87	104	90	94	99	93
T.H.	93	96	89	90	110	96
A.C.	94	97	92	83	105	87
A.C.	100	92	92	84	101	85
H.M.	92	100	93	91	101	92
H.M.	97	96	93	99	97	95
Mean	91.4	99.8	90.8	92.1	100.6	92.2
Stand. dev.	5.6	5.3	2.4	5.2	4.5	3.7
Std. dev. of mean	1.8	1.7	0.7	1.7	1.4	1.2

Values in percentage of control periods on air taken before and after the oxygen period.

find that in our trained subjects using continuous pressure breathing, and in all our subjects using intermittent pressure breathing, the cardiac output appeared to be reduced in proportion to the mean pulmonary pressure. This is in agreement with the results reported by Richards (5), with the direct Fick method. We have no similar confirmation of our results with forced breathing where a slight decrease in cardiac output also was found. This is contradictory to the results reported by Grollman (8) with the acetylene method, but may nevertheless be correct for our experimental conditions. There are so many conflicting chemical and mechanical factors involved in forced breathing that either result might be expected according to the exact pattern of the breathing.

The respiratory and circulatory effects of substituting pure oxygen for air are more uniform and indicate a 5 per cent increase in the minute volume of the ventilation and an 8 per cent decrease in the heart rate and cardiac output. Speculation concerning the mechanism of these effects seems futile because of the many possibilities which present themselves. However, it might be pointed out that the initial stimulus presumably depends upon the increased pO_2 in the arterial blood. Because of the decreased cardiac output, as well as the increased rate of oxygen consumption reported by Behnke, *et al.* (12), the mean pO_2 in the tissues would not be expected to change very much. The result, however, may depend more upon the response of the cerebral circulation to pure oxygen, and this may be quite different from the average for the whole body.

SUMMARY

(*1*) Records were taken with a ballistocardiograph to show the effects on the circulation of variations in intrapulmonary pressure or alveolar carbon dioxide tension, and of pure oxygen inhalation in place of air. The results are interpreted tentatively in terms of cardiac output.

(*2*) Breathing against a continuously elevated pulmonary pressure decreases the stroke volume but increases the heart rate. Compensation may or may not be complete.

(*3*) Breathing against a pulmonary pressure which is elevated only during inspiration decreases the stroke volume, in proportion to the mean pulmonary pressure, as well as the heart rate, so that the cardiac output is decreased to 85 per cent of normal.

(*4*) In voluntary hyperventilation of approximately the same volume as in (*3*) the cardiac output is diminished to 95 per cent of normal, the stroke volume being decreased and the heart rate increased.

(*5*) An increase in the dead space caused no consistent effect on cardiac output.

(*6*) Substitution of pure oxygen for air in normal breathing resulted in an increase of 5 per cent in the volume of the ventilation and a decrease of 8.5 per cent in the heart rate and cardiac output.

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CHANGES IN THE PNEUMOTACHOGRAM DURING POSITIVE PRESSURE BREATHING

by

Murray B. Sheldon Jr. and Arthur B. Otis

With continuous positive pressure breathing, inspiration becomes passive and expiration active – the reverse of the usual situation in normal breathing. Certain aspects of this phenomenon have been presented previously (1), but no detailed description of the alterations in the pattern of flow of respired gas that occur seem to have been published. The material presented below is a study of changes produced in the pneumotachograms of four subjects by application of continuous positive pressure breathing.

METHODS

The subject lay supine in a Drinker respirator and with a nose-clip applied breathed through a mouthpiece connected by a 55 cm. length of 3/4 inch inside diameter plactic tubing to a pneumotachograph. The latter utilized a disc of 400-mesh monel gauze which offered a resistance of 1 mm. H_2O at a flow velocity of 200 cc/sec. Recording of the differential pressure from this flow meter was done by means of a strain gauge pressure transmitter (Statham Laboratories) connected to a carrier wave amplifier, from which the rectified output fed into a galvanometer of an oscillograph (Hathaway Instrument Co.) loaded with six inch wide photographic paper. Typical records are shown in Figure 1. Calibration of the deflections on the record was accomplished at the end of each experiment by placing a Flowrater (Fischer and Porter Co.) in series with the pneumotachograph and making connection with an air line.

Pressure breathing was administered by adjusting the pump system of the respirator so that it produced a steady negative pressure within the respirator. Since this procedure made the intrapulmonary pressure positive with respect to that surrounding the body of the subject, it was mechanically equivalent to positive pressure breathing (+ P.B.). The general procedure with each subject was to obtain a record of normal breathing and then records during the administration of 20, 30 and 40 cm. H_2O + P.B. Each pressure was applied for a period of from 3 to 5 minutes, and a record was made during the last minute in each case.

The subjects studied were four healthy males between 25 and 35 years of age. Each subject was run through the test procedure twice on different days.

RESULTS

A series of recordings obtained on Subject R. is shown in Figure 1. In the absence of pressure breathing, all four subjects showed smooth rounded inspiratory patterns, such as those illustrated in this figure, whereas expiratory patterns tended

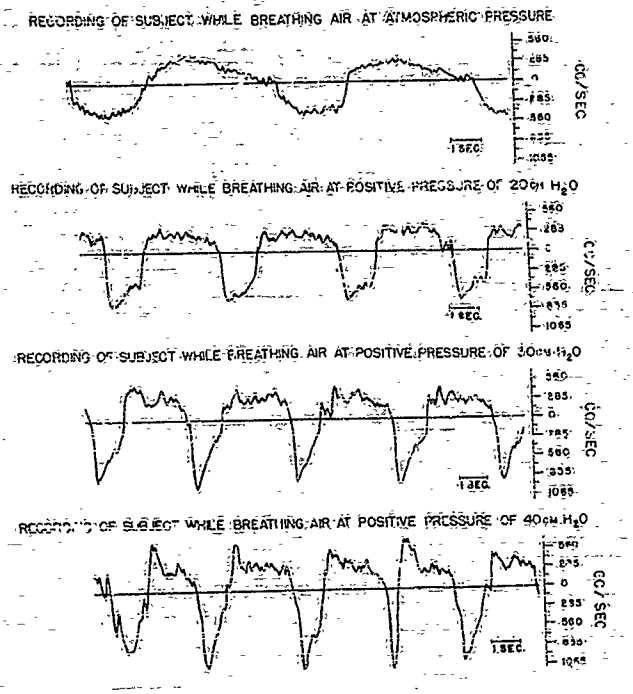

Figure 1

Pneumotachogram of normal subject (R) during breathing at atmospheric and at various positive pressures. In each recording, the curve below the reference line represents inspiration and that above the line expiration.

as a rule to be slightly more sharply peaked. These observations are consistent with those of Bretschger (2) on normal subjects, although his expiratory patterns were usually more markedly peaked than ours. This difference may be due in part to the fact that his subjects were sitting whereas our were supine. With positive pressure the inspiratory curves of our subjects became markedly pointed while the expiratory pattern appeared more rectangular with a broad plateau.

With positive pressures of 30 cm. H_2O or greater the expiratory pattern consistently showed an abrupt termination similar to that observed by Silverman (3) and by Cain and Ot's (4), when an artificial resistance to expiration was imposed. Similar expiratory patterns were observed by Silverman in the case of four asthmatics. It appears, therefore, that an increased opposition to expiration, whether it be produced by a mechanical resistance, by positive pressure or by a pathological condition, tends to produce a plateau-like configuration of the expiratory pneumotachogram.

All subjects experienced a definite subjective desire to hyperventilate while breathing positive pressure, although actual hyperpnea was absent in some instances. This dyspnea seemed to be progressive with increases in pressure and with duration of exposure. Mild fatigue attributable to the increased expiratory effort was noted by the subjects after the tests.

Quantitative information derived from the pneumotachographic records is indicated in Table 1 where the values shown for each subject are averages of

TABLE 1

INDIVIDUAL AVERAGES OF 2 TESTS

Pressure Applied cm. H_2O	Subj.	Time of Insp. secs.	Time of Exp. secs.	Cycle Time secs.	Peak Insp. Flow cc/sec	Time to Peak Insp. Flow secs.	Peak Exp. Flow cc/sec	Time to Peak Exp. Flow secs.	Mean Tidal Vol. cc.	Breaths per minute	Ventilation liters/minute
0	R.	2.77	4.61	7.38	500	1.34	368	1.09	993	8.1	8.04
+20	"	1.32	2.85	4.17	667	.34	368	.74	925	14.4	13.32
+30	"	1.22	2.47	3.69	735	.38	391	.70	663	16.3	10.81
+40	"	1.24	2.32	3.56	894	.44	504	.64	767	16.8	12.89
0	S.	3.09	4.74	7.83	460	1.42	354	.97	1008	7.7	7.76
+20	"	3.22	5.39	8.61	827	1.01	1036	.62	1864	7.0	13.05
+30	"	2.88	5.50	8.37	1314	.48	989	.31	2298	7.2	17.85
+40	"	2.73	4.96	7.69	1374	.50	988	.51	2100	7.8	16.38
0	C.	2.85	4.97	7.83	409	1.28	580	.88	955	7.7	7.35
+20	"	1.96	2.87	8.04*	515	.57	582	.78	822	7.5	6.17
+30	"	1.70	1.55	6.54*	712	.27	693	1.00	831	9.2	7.65
+40	"	1.50	1.43	8.51*	893	.30	666	1.08	823	7.0	5.76
0	B.	2.00	2.11	4.11	504	.71	595	.69	986	14.6	14.40
+20	"	1.48	1.92	3.40	687	.67	611	.51	896	17.7	15.86
+30	"	1.51	1.77	3.28	829	.55	530	.83	810	18.3	14.82
+40	"	1.70	1.94	3.64	676	.47	538	1.19	915	16.5	15.10
0	Aver.	2.68	4.11	6.79	468	1.19	474	.91	968	9.5	9.39
+20	"	2.00	3.26	6.06	674	.65	649	.66	1127	11.7	12.23
+30	"	1.83	2.82	5.47	898	.42	651	.76	1451	12.8	12.78
+40	"	1.79	2.66	5.85	959	.43	674	.36	1151	12.0	12.53

* Indicates that post inspiratory pause has been included

measurements made on three to seven breathing cycles from each of the two cycles. The tidal volumes were obtained by planimetric integration of the records.

These data reveal that on the average positive pressure breathing increases the ventilation and does so by an augmentation of both frequency of breathing and tidal volume. Time of inspiration and time of expiration are both decreased, as is the time required to attain peak flow in both phases of the breathing cycle. The peak flows themselves are increased.

Comparison of the separate data for the four subjects shows wide individual variations in the magnitudes of the various factors and neither in any individual case nor on the average are any of the observed changes directly proportional to the applied pressure. The quantity that changes most consistently with applied pressure is the peak inspiratory flow, which in each individual increases progressively with increasing pressure, a single datum excepted.

Rahn et al (5) have previously observed that during positive pressure breathing the lung volume does not increase as much as would be expected from the mechanical properties of the chest but that there tends to be a reflex opposition to expansion. It is probable that the large individual variations noted above are due rather more to differences in the voluntary or reflex response to P.B. rather than to differences in the mechanical properties of the chests and lungs of the subjects. Whatever their cause the variations are so great that a large series of subjects would have to be studies before any valid quantitative generalizations could be made.

SUMMARY

Pneumotachograms were recorded on four normal subjects breathing air at atmospheric pressure and under positive pressures of 20, 30 and 40 cm. H_2O. The inspiratory patterns became more peaked and the expiratory patterns more rectangular in shape. On the average, positive pressure breathing shortened the time required for inspiration and for expiration, increased the peak flow in both phases of the breathing cycle especially in inspiration, and increased the total ventilation. Individual variations in the measured quantities were large.

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REFLEX RESPIRATORY STIMULATION BY CHEST COMPRESSION IN THE DOG

by

George A. Culver and Hermann Rahn

The importance of reflex stimulation of respiration as a resuscitative measure has been discussed by Thompson and Birnbaum (1), and more recently by Whitehead and Draper (2) and by Bakos and Howell (3). Powerful reflex mechanisms produced by mechanical inflation and suction of the lungs were reported by Thompson and Birnbaum to be effective in resuscitation of dogs in asphyxial states. Whitehead and Draper reported ventilation stimulation by minimal pressure over the common tendon of the rectus abdominis and scalenus medius muscles of dogs anesthetized to the stage of complete respiratory arrest. Bakos and Howell observed significant pulmonary ventilation increases of dogs under deep barbiturate anesthesia by thorax constriction with a pneumatic cuff.

This study was undertaken to determine (1) the importance of the anesthetic level, (2) the effects of different degrees of lung deflation and (3) the role of the intact vagus on the respiratory responses elicited by compression of the chest and to describe any changes in a quantitative fashion.

METHOD

Dogs weighing from 10 to 32 kg. were anesthetized with sodium pentobarbital intravenously 1 cc./5 lbs. body weight. Continuous recording of respiration was accomplished with an oxygen filled Benedict-Roth metabolometer containing a carbon dioxide absorber. Air tight connection between the trachea of each animal and the apparatus was made with a cuffed endotracheal tube.

Thorax constriction and corresponding decrease in lung volume was produced in the first group of experiments by encircling the thorax with ordinary blood pressure cuffs and inflating as described by Bakos and Howell.

In all the remaining experiments chest compression was accomplished by inducing negative pulmonary pressure. The body was enclosed in an early model Drinker respirator capable of developing continuous positive pressure in the box. This method was felt to be superior to the cuff method since it produced a uniform pressure over the whole chest; thus the stimulus is identical during all repeated trials. Spontaneous respiration was interrupted for 30 seconds out of every 3 minutes with 10 cm. of water positive pressure in the box.

Reversible vagal block (part IV) was accomplished either by infiltration around the cervical vagi with 2% procaine hydrochloride solution in the region of the larynx or by direct cooling with circulating ice water through a small lead tube encircling each nerve.

OBSERVATIONS

1. Response to Different Pressures:

Mark et al (4) showed that about 30 minutes after injection of a barbiturate, the plasma concentration or anesthetic level can be considered relatively constant over a short period of time. During such a period of relatively constant anesthesia various cuff pressures were applied. The average response of three dogs is shown in Fig. 1. As the cuff pressure increases, tidal volume diminishes; however, respiratory rate increases, being greatest for an intermediate range of pressures applied. The net result in terms of total ventilation (minute volume) is an increase up to a pressure of 30 cm. H_2O or a lung volume decrease of about 90 cc. and then progressive decrease until pressures are reached producing actual reduction in total ventilation. In all of these experiments, the ventilatory response induced by compression (30 seconds) is compared with spontaneous respiration immediately preceding each cuff inflation. This induced response is expressed as percent of spontaneous respiration. Compression of the chest reduced the midcapacity lung volume, and this change is expressed in absolute values in Fig. 1, and is measured quantitatively from the base line shift on the metabolometer record similar to that in Fig. 2.

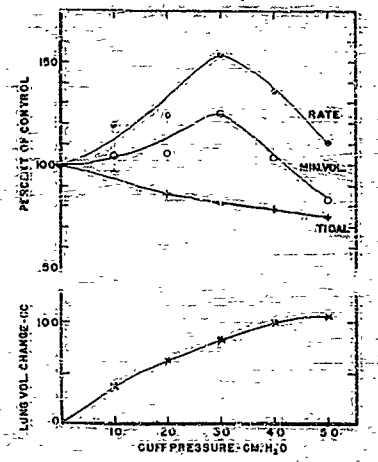

Figure 1

The effect of varying the cuff pressure around the chest upon respiratory response. Average of 3 dogs.

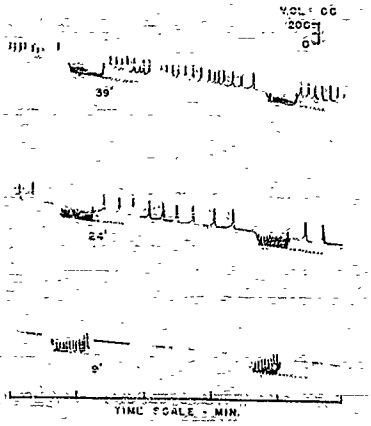

Figure 2

Samples of the spontaneous respiratory pattern recorded on a metabolism apparatus. The numbers indicate the absolute time in minutes after injection of pentobarbital. Every 3 minutes a negative pulmonary pressure of 10 cm H_2O is applied for 30 seconds. In addition to the ventilatory response which follows it can be seen that the lung volume displacement is altered with time.

II. Responses during Different Levels of Anesthesia:

Both the pattern of respiration and the quantitative responses were strikingly influenced by the depth of anesthesia. While in the foregoing experiments records are obtained during comparable stages of anesthesia, the results of these experiments were compared with the time elapsed after injection of sodium pentobarbital. In this study the negative pulmonary pressure technique was employed in supplying a positive pressure of 10 cm. in the Drinker respirator for 30 seconds out of every 3 minutes. This stimulus was applied for at least 2 hours after injection.

Fig. 2 shows the metabolometer record of a typical dog during the first 40 minutes breathing oxygen. Spontaneous respiration is completely absent in the beginning but oxygen uptake continues by "diffusion respiration". It is of particular interest to note that during this period chest compression will immediately induce respiration. The degree of lung volume change evoking this response is indicated by the depression of the sloping base line. During the 5th minute the lung volume is decreased almost twice as much as at the 39th minute when subjected to the identical pressure. The induced tidal volumes are at first large and slow while later they become small and more frequent.

The exact quantitative changes induced by 10 cm H_2O of negative pulmonary pressure are shown in Fig. 3. These curves represent the average response of 4 dogs each anesthetized with one grain of sodium pentobarbital per 5 lbs. body weight. The total spontaneous minute volume, induced minute volume, and the ventilation ratio (the induced over the spontaneous ventilation) as well as lung volume decreases are plotted against time in minutes after injection of the barbiturate. The spontaneous ventilation is measured during the 30 seconds immediately preceding each stimulation. It is of interest that both minute volume curves have a similar trend, both increasing as anesthesia lightens, while the percentage of stimulation or ventilation ratio decreases. Usually, the larger induced minute volume is achieved by an increase in rate only with a small reduction in tidal volume. The exact pattern, however, varies and is characteristic for each dog. The lung volume changes produced by the pressure also decrease with time as the central nervous system depression diminishes.

III. Vagal Block:

Bilateral cervical vagal block induced by ice water or procaine infiltration is followed by a slowing of the spontaneous breathing rate and an increase in the tidal volume. The resulting minute volume as well as the alveolar ventilation are actually increased. The relative hyperventilation induced by the vagus block must lower the arterial CO_2 tension considerably and suggests a normal inhibitory action of the vagus on the chemical respiratory drive under the conditions of these experiments. The results obtained on six dogs is shown in Table 1 (Column 1-4).

When 10 cm. of negative pulmonary pressure is applied after vagal block there is little change from the spontaneous respiration pattern of the vagus blocked animal and the average minute volume remains effectively unaltered. Compare columns 2 and 4, and 6 and 8. This proves the effectiveness of the block. During the control periods the spontaneous minute volume was changed from 610 cc. to 1030 cc. by the

TABLE 1

Dog	Vagal Block Induced By	Spontaneous Respiration Rate/min. C* 1	B* 2	Tidal Vol. cc. C 3	B 4	Respiration with 10 cm. H_2O Negative Pulmonary Pressure Rate/min. C 5	B 6	Tidal Vol. cc. C 7	B 8	Lung Vol. cc. C 9	B 10
1	Cold	8	7	30	30	10	7	40	40	40	40
2	Cold	6	4	80	120	7	5	70	100	80	100
3	Cold	5	5	60	120	7	5	70	120	40	50
4	Cold	2	3	110	200	7	4	80	120	10	40
5	Procaine	5	3	200	420	16	4	140	340	120	220
6	Procaine	2	1.5	300	500	8	4	280	440	110	200
AVERAGE		4.7	3.9	130	232	9.1	4.8	113	193	66	108
Minute Volume Computed from Averages		Control		610 cc.		Control		1030 cc.			
		Block		905 cc.		Block		925 cc.			

* C-Control
B-Block

pressure stimulus and this increase is of the same order of magnitude as that described in the previous section and Fig. 2.

One other finding is of interest, namely the change in resistance of the chest to the applied pressure before and after blocking the vagi. It can be seen (column 9 and 10) that with 10 cm of negative pulmonary pressure the lung volume is reduced on the average 66 cc, but after blocking the vagus 108 cc. This would suggest that the vagi play a role in the maintenance of the chest tone.

[Chest tone as used in this connection implies the net tonic activity of all the various respiratory muscles, including the diaphragm and intercostals, which determines the change of lung volume for a given pressure change. It has been described in man as the relaxation pressure curve (16)].

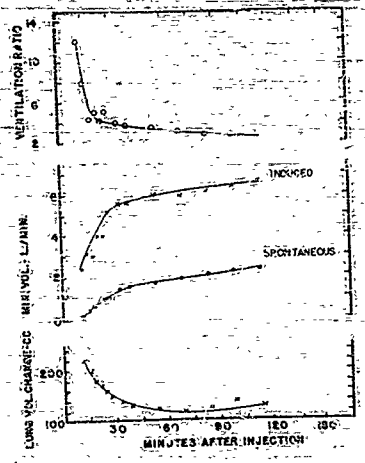

Figure 3

Changes in spontaneous and pressure induced minute volume as well as their ratio (ventilation ratio) with time after injection of pentobarbital. Lower curve indicates the changes in lung volume displacement with pressure breathing. Average values for 4 dogs.

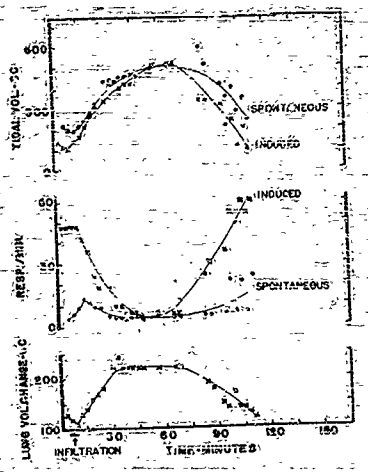

Figure 4

A "slow motion" picture of events during vagus block. Infiltration of the vagal region was begun at 5 minutes and complete block was realized about 30 minutes later. Recovery from block began about 70 minutes.

Blocking of the cervical vagi seems to be completely effective in eliminating the chest compression respiratory response. Procaine infiltration in one of our experiments acted slowly so that the complete block was not achieved until approximately 45 minutes after the initial injection. This made it possible to study the transitional changes of vagal block in "slow motion" (Fig. 4). It can be seen that

that the initial changes which occurred in lung volume, rate and tidal volume measurements were reversed at the end of 10 minutes when procaine infiltration began. Complete block seems to have been achieved between 50 and 60 minutes when the pressure application of 10 cm. H_2O produced no significant change compared to the spontaneous respiratory pattern. Recovery was accomplished after approximately 100 minutes.

Blocking each vagus separately with cold in the four cases studied by this method seems to indicate that the reflex stimulation is predominately associated with the right nerve, as its interruption eliminates almost entirely the typical response from compression of the chest, while block of the left vagus alone has little or no effect on this response.

DISCUSSION

The foregoing observations corroborate the findings of others (3) (10) (17) that respiratory stimulation produced by chest compression is mediated by the vagus nerve. According to Breuer (5) and Hering (6) the stretch receptors of the lung initiate the act of inspiration upon deflation of the lung and the act of expiration upon inflation. Instead of this self regulatory act with each respiration Hess (7,8) considers these proprioceptors responsible for a chronic reflex drive where a particular lung volume induced a certain diaphragm tone and thereby regulates the depth and frequency of respiration. The smaller the lung volume, the greater the diaphragm tone, the higher the frequency of respiration and the smaller the tidal volume. On the other hand, Gesell and Moyer (9) view the stretch receptor as purely excitatory, stimulating either the expiratory or inspiratory half center according to the phase of respiration.

Proprioceptive reflexes which arise in the chest wall were demonstrated by Fleish (12), Hammouda and Wilson (13), and Sharpey-Schafer (14), but apparently contribute very little to the gross respiratory response following chest compression. Whitehead and Draper (2) have recently reported that stimulation of respiration can be produced by localized pressure on the common tendon of the scalenus medius and rectus abdominus tendon. The result was not due to lung compression because the pressure was not sufficient to decrease the lung volume by more than 2 cc. In spite of repeated attempts on many different animals we were unable to elicit this reflex.

By tilting dogs from the head-up position to the head-down position Read and Scott (11) were able to shift the abdominal viscera and alter the relative lung volumes. The respiratory rate was increased in the head-down position and vice-versa. Bilateral cervical vagotomy abolished these responses. The curious fact that this reflex mechanism is primarily mediated over the right vagus nerve (Saris, Reed and Scott 10) was also confirmed in our experiments.

The degree of respiratory stimulation by chest compression seems to be determined by several factors. As seen in Fig. 1, there is an inverse relationship between the tidal volume and the external pressure applied. More significant, however, is the pressure which yields the optimal breathing rate. During the initial stages of decompression (Fig. 3) the stimulation, as judged by the ventilation ratio,

is far greater than during the later stages of recovery. In spite of the fact that the larger induced minute volume is achieved almost entirely by increase in respiratory rate and not tidal volume, the effective alveolar ventilation is increased. This can be calculated by assuming various sizes of the dead space (up to 130 cc.) and computing the effective alveolar ventilation during spontaneous and induced respiration. In addition, a few preliminary experiments were executed in which the alveolar O_2 and CO_2 concentrations were recorded continuously during spontaneous and pressure induced respiration by the method of Rahn and Otis (15). These showed an immediate rise in alveolar O_2 and a fall in alveolar CO_2 when pressure breathing was initiated. Thus, one may conclude that the chest compression, as carried out in these experiments, actually increases the effective (alveolar) ventilation at least during intermittent periods lasting 30 seconds. Particularly during the initial stages of deep respiratory depression this method should prove of value in preventing excessive retention of CO_2 and respiratory acidosis.

Of interest is the necessity of the intact vagus nerve for the maintenance of at least part of the tone of the chest cage. The relaxation volume pressure curve of the whole chest (16) must therefore be partly determined by a tonic reflex drive mediated over the vagus. This chest tone is reduced by vagotomy (Table 1, Figure 4, as well as by deep anesthesia (Fig. 2). The study of Hess (7) has shown that this tone is in part due to diaphragm activity. Whether or not the other respiratory muscles are also involved remains to be shown. The possibility of the vagi themselves being also efferent and acting on the smooth muscle throughout the lungs, thus altering tone and elasticity, must also be considered. The similar loss of elastic tone during very deep anesthesia suggests two mechanisms; one related to generalized muscular relaxation associated with profound central nervous system depression, and also a specific depression of the vagal center, amounting to vagotomy, by the general anesthetic.

This study suggests that the practical application of chest compression in resuscitation is limited to utilization of a relatively narrow range of pressures primarily during deeper stages of central nervous system depression. The reflexes involved may well be important factors in manual thorax pressure methods of artificial respiration, mechanical suck and blow, and body cabinet type of resuscitators and respirators. Any method of resuscitation dependent on the elastic recoil of the chest will certainly become more and more ineffective as central nervous system depression progresses or with interruption of the vagal mechanism.

SUMMARY

1. Ventilatory stimulation by chest compression was induced by negative pulmonary pressure breathing in dogs under deep sodium pentobarbital anesthesia. Bilateral and frequently right vagus block alone abolished this reflex.

2. The degree and pattern of the respiratory response following chest compression by negative pressure depends upon the level of anesthesia and the applied pressure. During complete respiratory arrest, while breathing oxygen, ventilation may be induced at any time by this method.

3. The lung volume displacement for a given negative pressure was greater the deeper the anesthesia. Vagotomy, at any stage of anesthesia, likewise produced a larger volume to pressure ratio indicating the importance of the vagus for the maintenance of chest tone.

4. The application of chest compression in resuscitation is discussed.

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Physiological Observations on Hyperventilation at Altitude with Intermittent Pressure Breathing by the Pneumolator[1]

WALLACE O. FENN, HERMANN RAHN, ARTHUR B. OTIS AND LEIGH E. CHADWICK.

THE PROBLEM of the subject at high altitudes is to regulate the breathing in such a way that the available pressure is divided between oxygen and carbon dioxide in the most advantageous manner. The natural response to this anoxic stimulus is an increase in the ventilation of the lungs and a reduction in the alveolar CO_2 tension.

In a series of performance tests with varying degrees of hyperventilation we have shown that there is no serious reduction in score until the pCO_2 in the alveoli is reduced below about 25 mm. Hg (1). In another series of tests carried out at a wide range of oxygen and carbon dioxide tensions we have been able to separate the effects of hypoxia and hypocapnia (2). The results indicate that most of the impairment of performance observed at high altitudes is due to the oxygen deficiency rather than the low CO_2. It appeared further that the amount of hyperventilation instinctively resorted to is probably not far from the optimum although in individual cases there may be either too much or too little ventilation over wide ranges. It seemed probable also that the optimum ventilation was different for different functions or types of performance test. In another study of survival at 25,000 feet breathing air (3) we have shown that under these extreme conditions the maintenance of consciousness is prolonged by a volume of ventilation somewhat in excess of that instinctively used by many of our subjects.

In the present paper, we wish to report briefly the results of 22 simulated flights to 46,000 feet using either continuous pressure breathing with natural volume regulation or intermittent pressure breathing with a relative hyperventilation. During these flights we obtained data on the alveolar carbon dioxide tensions as well as figures for the alkaline reserve and lactic acid content of the blood, and the excretion of base in the urine. The apparatus used in these flights for intermittent pressure breathing was the 'pneumolator'[2] the characteristics of which will be described by way of introduction.

[1] This work was done under contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Rochester. For further support since 1946 we are indebted to a contract with the Air Materiel Command, Wright Field.

[2] The pneumolator used in these experiments was designed by Mr. J. H. Clough of the General Electric X-Ray Corporation who kindly loaned it to us for this study.

Characteristics of Breathing on the Pneumolator. With this apparatus the lungs are inflated to a peak pressure the magnitude of which can be varied by a screw adjustment. When this pressure is reached an expiratory gate is automatically opened which permits the air to leak out until the ambient pressure is restored in the apparatus. The rate of expiration can be varied at will by a second screw adjustment which changes the size of the expiratory orifice. With these two adjustments the volume of ventilation can be varied over a wide range. A sample record of the pressure and the velocity of flow (measured with a pneumotachograph) as a function of time are shown in figure 1. The mean pressures averaged over the whole respiratory cycle were 35 to 45 per cent of the peak pressures, the figure being a little higher at the higher peak pressures.

It is important to note in figure 1 that the velocity of inflow is constant throughout the period of inspiration. This results from the fact that the chief resistance is in the apparatus itself where the pressure drop is from 50 lbs. down to the few inches of water which are necessary to maintain the same flow through the respiratory passages into the lungs. The volume of inflow

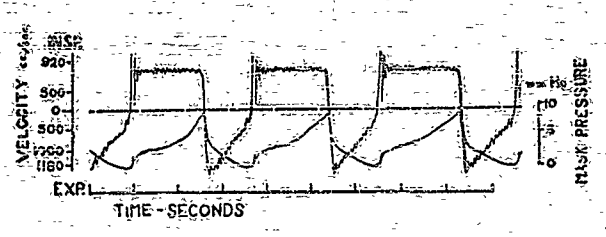


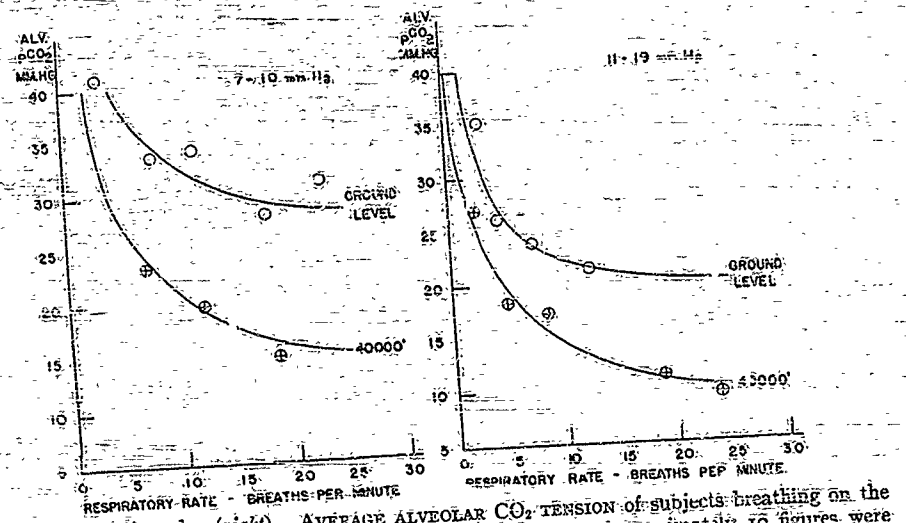
Fig. 1. Records of mask pressure and velocity of air flow while breathing on the pneumolator at a peak pressure setting of 5" of water.

and the duration of inflow should both depend only on the elastic capacity of the lungs and chest and the peak pressure setting. The pressure differential between the apparatus and the alveoli should be the same at all frequencies or peak pressures except during the transitional period when inspiration begins and is approaching a steady state of flow.

The minute volume of the ventilation when breathing through the pneumolator is increased above normal to varying degrees. Figures 2 and 3 show the alveolar CO_2 tension which results at 2 different peak pressures as a function of frequency and altitude. It is evident that doubling the frequency does not reduce the pCO_2 to half (chiefly because of the dead space). Further the pCO_2 is always much less at 40,000 ft. than at ground level.

Figure 4 gives a summary of average figures for the alveolar CO_2 at different altitudes using normal breathing at ambient pressure or pressure breathing of the continuous or intermittent type. The number of figures averaged for each point varies at the different altitudes but was in general between 10 and 100. The result is important in showing 1) that continuous pressure breathing using the standard pressure demand oxygen regulator neither increases nor decreases the normal ventilation; and 2) that the ventilation is

always greater and the alveolar CO_2 lower when intermittent pressure breathing is used. All three curves show a decrease in alveolar pCO_2 as the altitude increases. The figures are not suitable for exact interpretation because they



Figs. 2 (*left*) and 3 (*right*). AVERAGE ALVEOLAR CO_2 TENSION of subjects breathing on the pneumolator at 2 different peak pressure settings as indicated. Approximately 10 figures were averaged for each point. Intermediate curves (not shown) were also obtained at 30,000 and 35,000 feet.

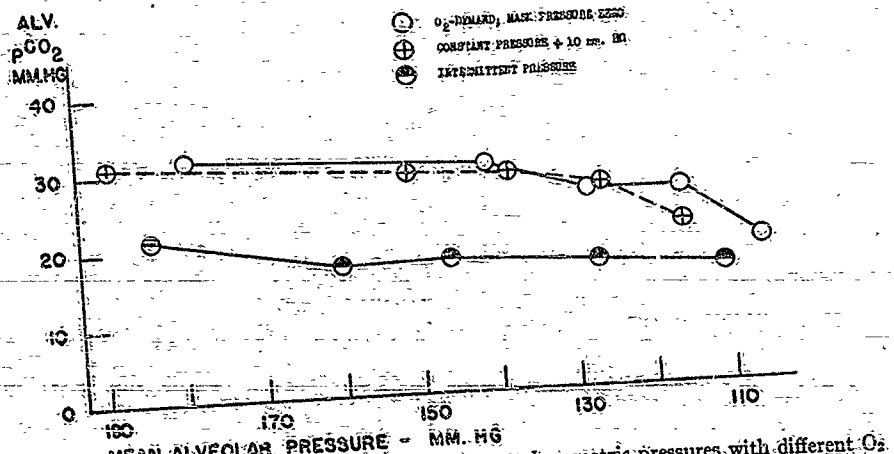


Fig. 4. MEAN VALUES for alveolar pCO_2 at different barometric pressures with different O_2 supply systems. Comparison of normal breathing, continuous pressure breathing and intermittent pressure breathing with the pneumolator.

represent many different subjects and many flights and varying durations of stay at each altitude.

The ventilation on the pneumolator is greater at altitude, partly because of the diminished resistance to the flow of gases. This is due to decreased

turbulence at low densities. Another reason for the increased ventilation depends upon the low pressure of the gas rather than its low density. Assume that the lung has a volume of V and does not expand while the pneumolator delivers a tidal volume of T and causes the pressure to rise from P to P + p. Then $(V + T) P = (P + p) V$ and $T = \frac{p}{P} V$. In this equation V and T are dry gas volumes in the lung and $P = B - 47$, where B is the ambient pressure. Thus for a given value of V and p, the tidal volume is inversely proportional to P, i.e. it increases with altitude. It is interesting to note also that if V = 3000 cc. and P = 81 mm. (40,000 ft.) a peak pressure of 13.5 mm. will provide a tidal volume, T, of 500 cc. Under these conditions the pneumolator will adequately ventilate the lungs even if the chest were somehow immobilized. Expansion of the lungs still further increases the ventilation. It is not surprising therefore that the ventilation at high altitudes not only increases when the pneumolator is used but may easily become excessive.

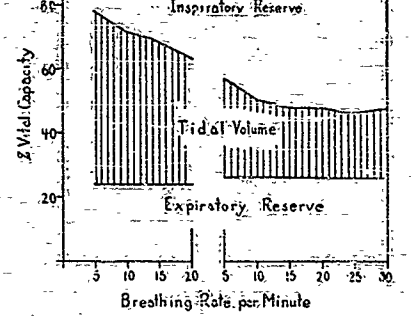


Fig. 5. AVERAGE TIDAL VOLUMES obtained with the pneumolator as a function of breathing rate (abscissae) at two different peak pressures. Shows a decrease in tidal volume caused by acapnia at the higher rates.

Another factor which determines the ventilation obtained with the pneumolator is the distensibility of the chest which varies in turn with the degree of acapnia. This is shown in figure 5 which illustrates the decrease in tidal volume which accompanies an increase in frequency of cycling of the pneumolator at ground level breathing air at two different peak pressures. If the lung and chest behaved entirely passively like a rubber balloon the volume of air needed for inflation to a given pressure would be the same at all frequencies.[3] In the lung however the decrease in pCO_2 in the alveoli which results from an increase in frequency seems to stiffen the chest reflexly so as to cause a progressive decrease in the tidal volume. The respiratory center is therefore able to control the ventilation to some extent in spite of the pneumolator.

[3] This is true only for an apparatus like the pneumolator in which the velocity of inflow is practically constant under all conditions. Since the rate of air flow through the trachea and the rate of expansion of the chest are constant the pressure gradient from apparatus to lung is independent of the frequency.

In these experiments it was not possible to measure the ventilation merely by passing the inspired gas through a gas meter before it reaches the mask because the pneumolator permits some gas to flow through the intake port even during expiration. At interval during the experiment, therefore, it was necessary for the subject to turn a large 3-way cock on the mask-intake exactly at the height of inspiration and collect one tidal volume in a small spirometer. While this volume was being measured by the observer the subject held his breath and then proceeded to blow out as much more air as possible, the expiratory reserve, which was again measured in the spirometer. These values are also included in the diagram of figure 5. It can be seen that the lung volume at the end of (tidal) expiration was slightly larger at the lower peak pressure even though ambient pressure prevailed in the lungs at expiration at all peak pressures. If this small difference is real it probably means that the increased reflex resistance to expansion developed at the higher peak pressure during inspiration continued to some extent during expiration.

The data for figure 5 were obtained from over 300 spirometer measurements on 7 different individuals. All the figures are calculated as percentages of the average vital capacity of 4750 cc. The individual variations lie within 10 per cent of the values indicated. All readings were taken after a period of adjustment. Figures for a given frequency were picked by graphical interpolation on a frequency vs. ventilation chart. At each new setting readings were taken every minute or two for 10 or 15 minutes and the results averaged before a new rate was established.

In another study of this same effect the subject lay supine in a Drinker respirator and breathed through a mask connected to a spirometer and a closed-circuit system with absorption of the CO_2 produced. Measurements were made of the normal ventilation of 8 subjects without using the respirator and again of the passive ventilation produced by the respirator at peak pressures of $+13$ and -25 cm. of water applied at a frequency of 15 per minute. After a period of adjustment a record of normal breathing was taken for 6 minutes followed immediately by a 15-minute record with the respirator going. Finally a period of recovery was also recorded. The results of these experiments were averaged together and are shown in figure 6. At both pressures the ventilation gradually decreased, the percentage decrease being 39 and 32 per cent for the two pressures as shown in table 1. This again seems to represent a gradual development of some reflex resistance to expansion.

In order to measure the rôle of acapnia in this progressive decrease in ventilation a second series of experiments was tried on 4 subjects in which the loss of CO_2 was prevented by an increase of 500 to 1000 cc. in the dead space of the rebreathing circuit. This increase in dead space was calculated so as to provide the same alveolar ventilation (and the same alveolar pCO_2) as that obtained in normal breathing. The results of these experiments are shown in figures 7 and 8. The curves show that the ventilation was better maintained when the acapnia was prevented. The decrease in ventilation in

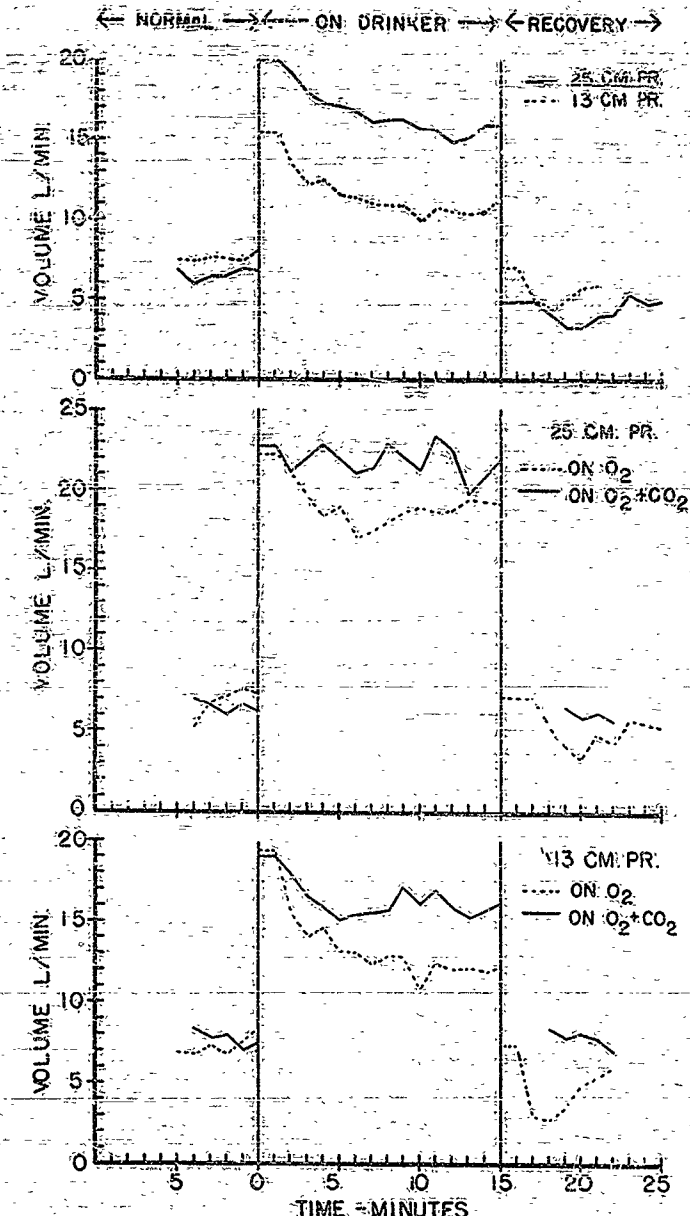


Fig. 6. (*upper*). AVERAGE MINUTE VOLUME of ventilation in 8 subjects, before, during and after a 15-minute period in the Drinker respirator at 2 different pressures applied intermittently. Abscissae, time in minutes.

Figs. 7 and 8 (*middle and lower*). AVERAGE VENTILATION of 4 subjects at 2 different pressures as affected by 15 minutes on the Drinker respirator. Solid line represents the same experiment with the addition of a dead space sufficient to prevent the alveolar CO_2 from falling.

per cent of the maximum values is given in table 1. The figures show that most but not all of the decrease may be attributed to the alkalinity of the over-

ventilation. The cause of the remainder is subject for speculation but it cannot be due to failure to prevent a fall in the alveolar CO_2 tension because alveolar samples were taken at the end of this hyperventilation period which gave approximately normal values of 37.4 and 36.6 mm. in two subjects at 13-cm. H_2O pressure and values of 39.5 and 38.5 for two subjects at 25-cm. H_2O pressure. The alveolar values for hyperventilation without added dead space were not determined directly but were calculated from the alveolar ventilation and the rate of CO_2 output and were found to be approximately 15 and 23-mm. pCO_2 for the 13 and 25-cm. pressures respectively.

In these experiments a record was available of every tidal volume and it was of interest to note the variations in the breathing patterns of different individuals. Some breathed with great regularity while others fluctuated

TABLE 1. AVERAGE PERCENTAGE DECREASE IN VENTILATION DURING 15 MIN. OF PASSIVE HYPERVENTILATION ON THE DRINKER RESPIRATOR (WITH STANDARD DEVIATION)

MEAN PRESSURE CM. H_2O	8 SUBJECTS NORMAL	4 SUBJECTS NORMAL	4 SUBJECTS WITH CO_2
−13	39 ± 14	47 ± 13	19 ± 12
−25	32 ± 22	23 ± 18	7 ± 18

The last two columns refer to the same 4 with and without added CO_2 (by increase of dead space).

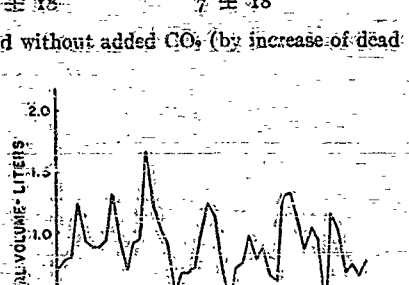


Fig. 9. RHYTHMICAL FLUCTUATIONS in tidal volumes at constant frequency of breathing on the Drinker respirator.

rhythmically over a rather wide range as indicated by the sample record in figure 9.

Theoretically, it should be possible to predict the total volume of ventilation which can be expected for a given peak pressure using the pneumolator or the Drinker respirator if the relaxation pressure curves (4) of the individual are known and the frequency of breathing. We have shown in these experiments however that acapnia in effect changes the position of the relaxation pressure curve or stiffens the chest so that it does not inflate to the expected degree. In 7 of the 8 subjects used in these experiments we have made careful measurements of the volume of the lung in percentage of the vital capacity at the height of inspiration. On the average the theoretical volume at 25-cm. H_2O pressure as calculated from the relaxation pressure curve is 87 per cent of the vital capacity. With continuous pressure breathing at this pressure the actual volume was only 80 per cent. With intermittent pressure breathing at the

same peak pressure of 25 cm. the volumes were 78, 72, 68, and 62 per cent respectively at rates of 5, 10, 15, and 20 breaths per minute. This decrease in inspiratory lung volume is another measure of the increasing resistance to inflation as the acapnia becomes more severe.

In some individuals a change in posture from sitting to supine changes the position of the relaxation pressure curve in such a way that a larger tidal volume would be expected for the same pressure change (25-cm. H_2O) in the pneumolator cycle. This was found to be the case in 2 out of 7 individuals the increases in tidal volume being 700 and 900 cc. respectively. This might become important in resuscitation operations.

Symptoms of Acapnia. In previous reports (1, 2) we presented the results of performance tests at different degrees of anoxia and acapnia. In general there was no appreciable decrease in score until the pCO_2 fell below 25 mm. so long as adequate oxygen was present. Anoxia combined with acapnia was worse than either alone.

The symptoms of acapnia as we have encountered them using the pneumolator at high altitudes have varied somewhat from one subject to another. If the ventilation rate is suddenly increased at an altitude of 30,000 feet or above, the alveolar carbon dioxide tension falls very rapidly and the subject may suffer an immediate attack of dizziness. If this dizziness is of such an intensity that it can be tolerated for a short time, it disappears. If the acapnia comes on more slowly, the dizziness may not appear at all and the first symptom will then be a tingling in the fingers or the toes. This tingling may become progressively worse until it extends up the legs to the waist or beyond. After this tingling continues for some time it also may disappear altogether in some subjects even though the alveolar pCO_2 continues to fall slightly. Thereafter the only symptoms of acapnia may be a slight tremor or unsteadiness or a deficient mental performance. In this stage the occlusion of the blood flow to the arm by a pneumatic cuff may bring on a spasm of the muscles of the arm. Along with the tingling there may be cold sensations in the legs and thighs or a feeling of tightness as if the tone of muscles was increased or as if the muscles were about to go into tetany. Some individuals experience tingling in the chest or face and one of our subjects becomes unable to talk intelligibly because of spasms of the facial muscles. Another of our subjects (*H.R.*) on two occasions has practically become unconscious from acapnia, failing to respond to signals and making glaring errors in his manipulations. He does not actually faint but simply sits upright, apparently normal but quite unresponsive. He has twice reacted, however, in exactly the same way at 50,000 feet while breathing from the pressure-demand system, an effect presumably due in this case to anoxia.

Tremor of the hands is a common symptom of acapnia which is clearly evident in the handwriting and is measured by the hand steadiness test previously described. In one subject, sleepiness and listlessness were the only

symptoms which we could elicit and these occurred in many subjects to varying degrees.

Simulated Flights to 46,000 Feet. In our small two-man chamber we have carried out 22 flights to this altitude one subject using the pneumolator and the other using the standard continuous pressure-demand system. Alveolar pCO_2 has been followed carefully in all cases.[4] Seven different subjects have reached the 46,000-ft. altitude and with one exception all have continued for one hour. One subject collapsed within about 10 minutes on 3 different trials. This was probably attributable to the effects of pressure on the circulation because the same subject collapsed at ground level from pressure alone 3 times and has tolerated considerably lower oxygen tensions without PB at 25,000 feet breathing air. In one flight both subjects reached 50,000 feet and remained conscious for 10 minutes but in two other flights attempts to repeat this performance necessitated emergency descents. Some performance tests were tried on these flights as a measure of the condition of the subject and these have been included in part in a previous report. Regardless of any such tests however it was clear both to the observers and the subjects that the man using the continuous pressure breathing was in a better condition and would be safer as the pilot of a plane than the more acapnic individual using the intermittent pressure breathing system. The results might have been different however if the pneumolator had been so adjusted as to prevent the alveolar CO_2 tension from falling below 25 mm. This result must not be taken to indicate therefore that all continuous PB is better than intermittent PP. The result will depend upon the particular settings and the particular apparatus used. In the Bennett valve for intermittent PB, for example, the pressure is allowed to fall only part way toward zero during expiration so that the mean pressure is considerably greater for the same peak pressure and the tendency to overventilation is less than that found on the pneumolator. This would probably be superior to continuous PB.

In our original report (5) all the experiments which we have done both at 46,000 feet and at other altitudes including those at 18,000 to 25,000 feet breathing air have been plotted in 8 separate charts like that in figure 10, one chart for each of our subjects. Solid symbols indicate that there were symptoms of acapnia or anoxia recorded while hollow symbols indicate that the

[4] Most of the alveolar CO_2 values recorded in these flights were obtained from samples drawn by a syringe from the expiratory tube of the mask after a forcible expiration. These were analyzed at once by the Scholander method in which a known volume of gas (about 10 ml.) is delivered by the syringe directly through a rubber tube into a vessel containing KOH, the unabsorbed volume being measured at ambient pressure in a 10 ml. graduated stem sealed to the vessel. In carrying out this analysis we found that the reliability of the results could be much improved if during the analysis the observer regulated the pressure in the chamber with extreme care by reference to a water manometer located inside the chamber. One end of this manometer terminated in an air reservoir which was cut off from communication to the chamber by a clip applied by the subject inside the chamber when the analysis was about to begin. With this arrangement the Scholander analyses were very uniform but for some unknown reason averaged 2 mm. below values obtained by analysis of samples taken over mercury and analyzed after descent on a Haldane apparatus.

subject appeared to be in good condition. Each diagonal line extending from the top to the bottom of the chart indicates a given altitude or ambient pressure (breathing pure oxygen) and the short slanting lines extending from some of the symbols down and to the left to an altitude diagonal indicate the increase in CO_2 and O_2 pressure which was obtained by pressure breathing. It can be seen that this increase from intermittent PB (small circles) was much less than the gain from continuous PB (large circles) because the mean pressure was less. In this particular subject there seemed to be no symptoms at alveolar CO_2 levels above 20 mm. and this was typical of most of our subjects (except *A.B.O.* who showed symptoms at 25 mm.). One of our subjects had a tendency to hypoventilate at 46,000 feet and felt better when he was urged to

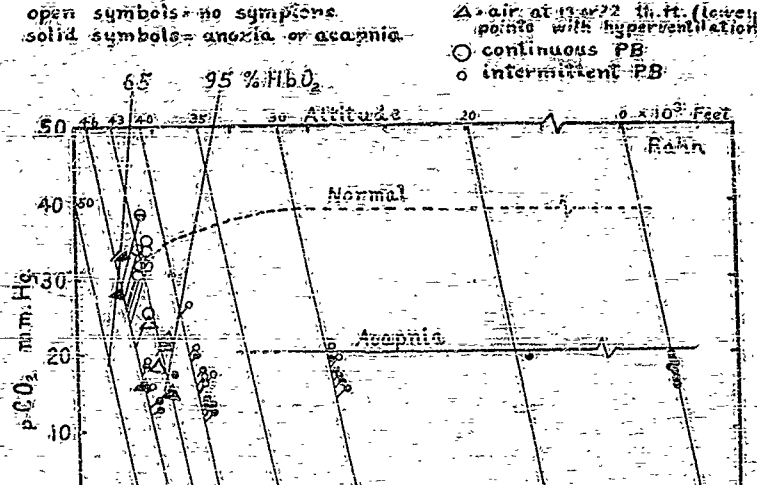


Fig. 10. Record alveolar pCO_2 and pO_2 on many flights by subject Rahn.

breathe more deeply. This shows again the supreme importance of obtaining an optimum breathing volume at altitude.

The dotted line in figure 10 for normal alveolar air was drawn in accordance with average results obtained in breathing without PB at different altitudes. Averaging 16 to 21 different flights the alveolar pCO_2 values at 30, 40, and 42 thousand feet were 39.0, 34.8, and 32.0 mm. Hg, respectively.

Finger temperatures were measured during these and similar flights to other altitudes. For this purpose the subject merely grasped between his thumb and finger a series of copper constantan junctions which recorded on a galvanometer outside the chamber. The results were somewhat variable due to the differing conditions of the subjects. In the subjects who were using the pneumolator the temperature fell in about half the cases. Anoxia alone ap-

parently had some tendency to cause cooling because a drop in finger temperature was observed in a third of the subjects using continuous PB at 46,000 feet and in half the subjects breathing air without PB at 18,000 feet. None of the subjects at 30,000 ft. breathing oxygen from the demand regulator (without pressure or anoxia) showed any fall in temperature. These results include some measurements made of toe temperatures by a thermocouple continuously in contact.

An attempt was made to confirm this suggestive evidence of vasoconstriction during hyperventilation by measurements of leg volume while hyperventilating with the pneumolator at ground level. The results were conflicting because of inadequately standardized conditions. In general it might be said that out of 10 experiments 5 showed a decrease in volume, 1 an increase and the rest showed no definite effect either way. A decreased blood flow through the hands during hyperventilation has been reported by Stewart (6) and by Schneider (7).

Chemical Compensations in Hyperventilation. Numerous studies of the effect of hyperventilation on the blood and urine have been recorded in the literature.

Increased alkalinity of the urine, suppression of ammonia excretion, and production of acetone bodies in the urine are known to occur (8–10). Peters *et al.* (11) observed an increase in the organic acid of the blood but found no change in the carbon dioxide capacity. Bock, Dill, and Edwards (12) reported an increase in blood lactate but found no appreciable change in the alkaline reserve. Davies, Haldane and Kennaway (10) also found that the carbon dioxide dissociation curve remains unaltered. Grant and Goldman (8) reported large decreases in the carbon dioxide capacity of plasma, but their measurements were made on plasma separated at the carbon dioxide tension existing when the blood was drawn and so indicate nothing as to any real change in the whole blood. Shock and Hastings (13) found an increase in the fixed acid of the blood if the overventilation persisted long enough. Gollwitzer-Meier (14) and Rapoport *et al.* (15) report an increase in chloride, a decrease in sodium and a rise or no change in potassium.

All the above experiments were carried out on subjects voluntarily hyperventilating, and, in most cases, for relatively short periods of time. Consequently, it seemed desirable for the study of survival at altitude to secure some measurements on subjects hyperventilating passively for an hour or more with the aid of the pneumolator. If such hyperventilation is performed at altitudes of 30,000 feet or above, it can be carried on with ease for long periods. At ground level, the greater resistance of the air (due to turbulence) is such that it is difficult to lower the pCO_2 to the point of evident acapnia in most subjects. The greater resistance occurs presumably at the oxygen inflow orifice in the pneumolator so that it is necessary for the subject to 'lead the machine' very much and produce large negative pressures on inspiration in order to obtain the necessary volume of ventilation.

The flights described above in which subjects remained for one hour or

more at simulated altitudes of 30,000 and 45,000 feet provided an opportunity of obtaining the data desired.

METHODS

Blood and urine samples were collected from the subjects just before they entered the chamber for a flight. The time of the latest previous urination was recorded. Samples were again collected when the subject emerged from the chamber following the flight. The blood samples were obtained from the cubital vein and placed in a flask containing 35 mg. of sodium fluoride per 10 ml. of blood. When it was not possible to begin the analyses immediately, the blood was stored in an ice bath.

Lactic acid was determined by the method of Barker and Summerson (1941). The carbon dioxide combining capacity was obtained by equilibrating the blood with a mixture of 4.8 per cent CO_2 and 95.2 per cent O_2 in tonometers at 38° C. and analyzing the equilibrated blood for CO_2 by the method of Van Slyke and Neill (1924).

The volume of each urine sample was noted and the *p*H was measured with a Beckman *p*H meter. As a measure of base excretion, an aliquot was titrated to *p*H 7.4 by addition of 0.1 N HCl or 0.1 N NaOH as required. The reading of the glass electrode was used to indicate the end point.

RESULTS

Results of the analyses are shown in table 2. For purposes of comparison the flights have been divided into four groups as follows: *1*) flights at 30,000 ft. with the subject breathing oxygen from a demand system; *2*) flights at 30,000 ft. with the subject breathing oxygen from the pneumolator; *3*) flights at 46,000 ft. with the subject breathing oxygen from the Pioneer Pressure-Demand System (continuous P.B.); and *4*) flights at 46,000 ft. with the subject breathing from the pneumolator.

In *groups 1* and *3* there was hyperventilation present only to the extent that it spontaneously occurred due to altitude, whereas in *groups 2* and *4* additional hyperventilation was imposed on the subject by the pneumolator. In *groups 1* and *2* there was no hypoxia. In *groups 3* and *4* varying degrees of hypoxia were present.

The results shown in detail in table 2 are summarized in table 3. The figures show that, on the average, with the pneumolator at either 30,000 or 46,000 feet there was an increase in lactic acid concentration, a decrease in bicarbonate CO_2 capacity and an increase in the rate of excretion of base in the urine. The increase in lactic acid concentration is presumably the direct result of an increase in the alkalinity of the blood caused by hyperventilation (12, 16, 17). When lactic acid is added to normal blood at constant carbon dioxide tension about $\frac{2}{3}$ of it is neutralized by loss of bicarbonate while the remainder is combined with base taken from the buffers of the blood. Since

at 39,000 feet on the pneumolator the addition of 1.5 mEq. of lactic acid to a liter of blood caused an average decrease of 1.0 mEq. of bicarbonate per liter of

TABLE 2. CHEMICAL CHANGES DUE TO HYPERVENTILATION IN SIMULATED FLIGHTS TO HIGH ALTITUDES

	SUBJECT	FLIGHT NO.	BLOOD LACTATE		CO_2 CAPACITY		pH OF URINE		ACID EXCRETION		URINE FLOW		ALVEOLAR PCO_2	OXIMETER
			Before	After	Before	After	Before	After	Before	After	Before	After		
			mEq/l.		*mEq/l.*				*mEq/hr.*		*ml/hr.*		*mm. Hg.*	*% sat.*
39,000 ft., O_2 demand	*HR*	137	0.8	1.1			6.42	7.65	0.3	−0.2	29	27	36	
	VS	142	1.8	2.4	19.2	18.4	5.50	5.52	0.9	1.1	18	34	35	
	VS	145	2.1	1.8	19.1	20.1	4.90	5.10	0.8	0.7	16	43	33	
	CB	140	1.3	2.0	20.5	19.5	5.77	5.10	0.7	1.0	30	36	34	
	Means.....		1.5	1.6	19.6	19.3	5.65	6.00	0.7	0.7	23	40	34	
39,000 ft., GE pneumolator	*WF*	125	2.4	3.9			5.91	7.05	0.9	0.1	45	47	25	
	HR	134	0.5	1.2	20.0	18.2	5.90	7.63	0.6	−1.2	27	70	43	
	CB	137	2.0	3.3	18.3	17.5	7.40	7.50	0.0	−0.1	72	72	19	
	HR	142	1.3	4.0	19.4	18.0	6.84	7.90	0.2	−0.4	37	49	22	
	RG	145	1.2	3.3	19.1	18.3	6.40	7.40	0.7	−0.8	177	132	20	
	JP	146	2.8	2.9	19.9	18.7	5.25	6.95	2.1	−0.2	36	60	21	
	WF	147	2.0	2.5	17.7	17.9	6.10	7.43	0.6	−0.2	40	69	17	
	RG	148	1.7	3.5	20.5	19.0	6.80	8.10	0.5	−0.6	24	38	24	
	CB	154	2.5	5.8	15.5	18.7	6.16	7.70	0.8	−0.7	59	46	16	
	Means.....		1.9	3.4	19.3	18.3	6.31	7.58	0.6	−0.5	57	70	19	
46,000 ft., PB demand	*ME*	138	1.9	1.7	18.5	19.1	5.35	5.93	4.5	0.9	103	36	34	65–70
	LC	139	2.0	1.3	17.8	18.1	5.30	6.68	1.7	−0.9	40	68	27	78–85
	AO	143	2.2	1.6	18.0	19.3	6.64	7.20	0.3	−0.1	58	54	30	60–80
	AO	144	2.9	1.4	19.2	19.6	6.45	6.95	0.4	−0.1	44	45	27	60–80
	HR	140	1.7	1.3	20.4	18.9	5.98	5.40	0.7	2.6	26	58	34	60–70
	ME	152	1.6	2.2	20.1	18.0	6.59	6.97	0.4	0.2	39	52	30	75–86
	HR	150	1.8	1.7	20.2	19.8	5.92	7.61	0.5	−0.3	44	46	28	65–75
	Means.....		2.0	1.6	19.2	19.0	6.06	6.73	1.2	0.3	52	51	31	
46,000 ft., GE pneumolator	*JP*	131	1.5	4.0	19.8	17.4	5.71	6.65	1.2	0.6	49	99	15	95
	CB	133	0.7	1.2	18.4	17.8	6.20	7.55	0.7	−0.6	45	75	19	80–91
	CB	135	1.5	1.6	18.5	16.7	6.12	8.10	0.7	−0.7	45	55	17	85–95
	AO	136	1.7	2.2	19.4	17.8	5.56	7.28	0.1	0.1	31	183	20	91–94
	JP	138	1.6	5.4	20.0	17.2	5.30	7.25	3.1	−0.6	99	143	16	93–95
	WF	139	2.2	2.5	17.8	15.9	5.80	7.40	0.6	−0.2	31	100	17	87–93
	HR	143	1.9	1.4	19.7	18.8	5.51	8.30	1.1	−1.1	35	54	21	85–95
	HR	144	1.5	4.0	19.0	18.8	5.45	7.61	1.0	−0.9	32	53	16	95–97
	ME	149	2.0	1.6	19.6	17.8	5.80	8.00	1.4	−0.1	34	46	18	80–97
	AO	152	1.8	3.9	19.7	18.6							19	85–93
	ME	156	2.2	3.8	20.5	17.8	6.25	7.61	0.7	−0.4	41	97	24	90–93
	JP	157	2.1	2.7	20.5	19.0	5.15	6.91	2.7	−0.2	57	110	28	90–94
	AO	160	1.8	3.0	20.9	18.6	5.79	7.40	0.4	−0.3	62	310	20	80–93
	Means.....		1.7	2.8	19.5	17.9	5.70	7.51	1.1	−0.3	47	110	19	

Oximeters were not used on the 39,000 foot flights.

[1] Since the column headed 'Acid Excretion, After' does not always appear to be consistent with 'pH of Urine, After', a word of explanation is necessary. The values for acid excretion are corrected for the time between 'before' and 'after' samples not spent at altitude. During this time which averaged 26 minutes, it was assumed that the rate of acid excretion was that indicated by the 'before' sample.

blood, it may be concluded that at this altitude the lactic acid is responsible for all of the change in the CO_2 dissociation curve of the blood. At 46,000 feet, however, the change in lactic acid concentration (+1.1 mEq/l.) accounts

for only about half of the bicarbonate change (−1.6 mEq/l.). Calculation shows that the increased excretion of base in the urine is too small to account for more than a small fraction of the remaining change in the bicarbonate so the presence of some other acid in the blood is to be suspected. A decrease in the excretion of ammonia might be another contributing factor as well as the decrease in sodium and increase in chloride reported by Gollwitzer-Meier (14) and by Rapoport *et al.* (15).

The exact mechanism by which the undesirable effects of excessive hyperventilation (numbness, tingling, tetany etc.) are produced is unknown, but it would seem that the fundamental disturbance is an increased alkalinity of the blood and tissues. It is of interest, therefore, to estimate the magnitude of the compensation that will be produced by the slight lowering of the CO_2 capacity found in our experiments.

TABLE 3. ACID-BASE CHANGES DURING HYPERVENTILATION AT ALTITUDES

pCO_2	% SATURATION	ALTITUDE	CHANGE IN CO_2 CAP.	CHANGE IN LACTIC ACID	CHANGE IN EXCRETION OF BASE	CHANGE IN URINE FLOW	C. OF EQ.
			mEq/l.	*mEq/l.*	*mEq/hr.*	*ml/hr.*	
37	96	30,000 ft. O_2 demand	−0.3	+0.1	0.0	+17	1
20	96	30,000 ft. Pneumolator	−1.0	+1.5	+1.1	+15	2
35	70	46,000 ft. P.B. demand	−0.2	−0.4	+0.9	−1	3
20	85	46,000 ft. Pneumolator	−1.6	+1.1	+1.4	+63	4

By the methods described in the *Syllabus of Methods from the Harvard Fatigue Laboratory*, approximate CO_2 dissociation curves have been constructed for our average pre-flight blood and for blood after hyperventilation at 46,000 feet. From these curves one can estimate that at a pCO_2 of 19 the original blood will have a *p*H of 7.63, while the blood after hyperventilation will have a *p*H of 7.60. Or, stated in a different fashion, the blood after hyperventilation will have the same *p*H at a pCO_2 of 19 as the original blood would have at a pCO_2 of 21. This is a very small compensation and falls far short of keeping the *p*H in normal limits.

The *p*H of our pre-flight blood at a pCO_2 of 40 is estimated to be 7.4. If the blood were to have the same *p*H at a pCO_2 of 19 the carbon dioxide capacity would have to drop by about 7.2 mEq/l. To accomplish this by production of lactic acid would mean increasing the lactate concentration of the blood by about 11.2 m Eq/l. This is 3 times the greatest increase we have observed in our subjects and 8 to 9 times the average increase. The formation of lactic acid which we have observed represents therefore a 10 to 20 per cent

compensation for the alkalinity of hyperventilation. This figure, however, is based upon blood samples taken immediately after the flight and it is possible that the lactic acid disappears rather quickly after the ventilation returns to normal. To lower the carbon dioxide capacity of the blood by 7.2 mEq/l. by excretion of increased amounts of base in the urine would require excretion of 36 mEq/5 l. × 7.2 mEq/l.) of base from the blood plus perhaps 5 times this amount from the tissues or a total of 180 mEq. At the rate of 1.4 mEq./hr. observed in our subjects at 46,000 feet this would require about 5 ½ days.

It should be noted that the chemical changes reported above refer to differences between two blood samples taken immediately before and immediately after the flight. The small size of our chamber made it inconvenient to take blood samples during the actual flight and it was felt also that this might interfere with some of the other measurements which we were making. In order to confirm some of the findings we carried out 5 experiments on hyperventilation at ground level. This was found much more difficult than at altitude on account of the greater resistance to air movement and it was necessary for the subject to make considerable efforts in order to keep the alveolar CO_2 tension in the neighborhood of 20 mm. for long periods of one hour. Three subjects reached 20 mm., one reached 25 mm. and one 30 mm. In the 4 who reached 25 mm. or below there was an increase in the lactic acid concentration of the blood of 0.5 to 1.5 mEq/l. which is in good agreement with figures of Bock *et al.* (12). In the other subject there was a slight decrease in lactic acid.

The changes in plasma potassium were scarcely significant although in three cases there was a slight fall, (av. 0.4 mEq/l.), in one case no change, and in one case where the hyperventilation was least, a rise. Rapoport *et al.* (15) reported a slight rise of 0.3 mEq/l. in 2–6 minutes of hyperventilation. Our hyperventilation lasted much longer but the changes were of the same order of magnitude although usually opposite in direction. On the whole it is difficult not to support the conclusion of Gollwitzer-Meier (14) that there is no significant change in plasma potassium under these conditions.

DISCUSSION

At an altitude of 46,000 feet the aviator has the problem of breathing deeply enough to avoid anoxia without breathing so deeply as to suffer the disadvantages of acapnia. Of the two dangers anoxia is the more insidious because it gives less warning and the threshold is sharper. Acapnia is a more gradual type of incapacitation and if it comes on slowly a very low carbon dioxide tension may be tolerated without serious consequences.

In subjective symptoms we have found that acapnia and anoxia are synergistic. This may not be true of all performance tests and it is not true of cerebral flow for the vessels dilate with anoxia and constrict with acapnia (18).

Hill and Flack (19) reported that the symptoms of acapnia resulting from ground-level hyperventilation could be prevented by the inhalation of oxygen. We have been unable to confirm this observation in a number of experiments carried out for this purpose. We also tried hyperventilation at ground level on air and on 9 per cent oxygen in nitrogen and seemed to find an earlier rather than a later onset of acapnia in the low oxygen mixture. As a more acute test we took one subject to 18,000 feet where he hyperventilated on the pneumolator breathing air. After signs of acapnia had appeared he changed abruptly to pure oxygen without changing the rate or depth of his breathing and experienced no perceptible change or alleviation in his symptoms. After another 15 minutes he changed back to air and failed again to notice any change in his condition. While these tests are not conclusive by themselves they do not encourage the idea that acapnia and anoxia are antagonistic in their effects on performance as they seem to be on the cerebral blood flow.

SUMMARY

Intermittent pressure breathing on the pneumolator results in hyperventilation and a lowering of the alveolar CO_2 tension. This hyperventilation is greater at altitude than at ground level because of the decreased resistance to air flow and because a larger tidal volume is necessary to produce the same peak pressure at the lower ambient pressure. The expansion of the chest during inflation with the pneumolator is not entirely passive. As acapnia develops the chest seems to expand less for the same pulmonary pressure. This is shown also by measurements of passive ventilation on the Drinker Respirator.

Simulated flights to 46,000 feet are described in which comparisons were made between continuous pressure breathing and intermittent pressure breathing. It was found that the higher oxygen tension and arterial saturation which resulted from the greater ventilation obtained on the latter system were not sufficiently advantageous to compensate for the lower mean pressure in the lungs so that under the conditions of these experiments the subjects preferred continuous to intermittent P.B. There is however a possibility that an intermediate system might be better than either. During these one hour periods of hyperventilation at high altitudes the alveolar CO_2 tension fell to 20 mm., the alkaline reserve of the blood fell 1.3 mEq/l. and the lactic acid concentration of the blood rose an approximately equivalent amount. The *p*H of the urine and the excretion of base also increased but the absolute amount of base lost in this way was not sufficient to have a significant effect on the alkaline reserve of the blood.

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Voluntary Pressure Breathing at High Altitudes[1]

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DURING THE WAR an emergency procedure for increasing altitude tolerance was suggested by Commoner (1) and was called Voluntary Pressure Breathing (VPB) or later Emergency Breathing Procedure. This procedure consisted in a quick inspiration followed for 2 seconds by the development of maximal intrapulmonary pressure with a closed glottis. At the end of this pressure period, the air in the chest was slowly expired. This cycle was repeated 12 or more times a minute. Theoretically, this increased pressure raised the mean oxygen pressure in the alveoli and so increased the saturation of the blood. This procedure was tested by Commoner in low-pressure chambers and in actual flights at 25,000 ft. and he found that it was possible to manipulate the airplane or carry out other routine procedures without the use of oxygen at this altitude provided the breathing was done according to his directions. In further practical tests Gemmill, Lillienthal and Riley (2) at Pensacola found a gain in altitude tolerance of 4000 feet and an improvement in conscious survival with VPB at 44,500 ft.

Following the publication of Commoner's report, we became interested in this subject and believed that most of the advantage attributed to VPB was actually due to the concomitant hyperventilation; see Chadwick *et al.* (3a). Houston *et al.* at Pensacola (4) and King *et al.* at Bethesda (5) came to similar conclusions. Commoner found no evidence of hyperventilation in the symptoms of his subjects but reported that the *p*H of the urine excreted during VPB was greater than normal.

In a later report, Commoner (6) reinvestigated the question and reported that hyperventilation was far worse than normal breathing on account of the severe acapnia which developed. It was evident that he permitted his subjects to increase their ventilation far too much so that the symptoms of acapnia were severe. The comparison was therefore invalid. This is true in general of most of the hyperventilation tests which have been made. It is indeed difficult even for experienced persons to attain an optimum degree of hyperventilation.

Some efforts to increase altitude tolerance by special breathing methods were also

[1] This work was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Rochester. For continued support since 1946, we are indebted to a contract with the Air Materiel Command, Wright Field, Dayton, Ohio.

tried in Germany and those are described by Schoedel (7) in his chapter in the Fiat Review of German Science. He mentions two patterns 1) with inspiration emphasized (Schnappatmung) and 2) with expiration emphasized (mountain climber's breathing). In the discussion Niggemeyer is quoted as believing that the first type is beneficial only because it prevents excessive loss of CO_2 but still increases the ventilation. Likewise Klostermann is quoted as stating that it is only the volume of the ventilation and not the pattern of the breathing which is responsible for the success. No actual data concerning the effectiveness of these procedures are available from this source.

During the war this subject was classified as 'confidential' and no review of VPB has yet been published. Since our own studies included careful measurements of the ventilation rate and the composition of the alveolar gas it seemed worthwhile to collect them in this paper for publication so that the rather important theoretical aspects of the problem can be clearly presented. Most of the other investigations of the procedure have involved merely service testing for military use and most of them have not included data on the actual degree of acapnia which was produced. All agree, however, in showing that this VPB procedure increases the saturation of the arterial blood as measured by the Millikan oximeter.

METHODS

Two series of experiments were carried out. In Series A there were 29 ascents in the pressure chamber to 18,000 ft. breathing air and 14 ascents to 42,000 ft. breathing oxygen. Thirteen subjects (one female) participated. Comparisons were made of VPB and hyperventilation (HV). In Series B there were 23 man runs to 25,000 ft. breathing air with somewhat more extensive measurements for the study of the causes of failure.

In the flights of Series A the subject adjusted his oximeter to 96 per cent saturation breathing air at ground level after a preliminary rest of 5 to 10 minutes and then began the 'ascent' at the rate of 5000 ft./min. After 10 to 15 minutes at the desired altitude with normal breathing (with O_2 at 25,000 ft. or above) a similar period of 10 to 15 minutes of VPB was begun. Following VPB and a 5-minute rest period with normal regulation of breathing a final period of 10 to 15 minutes was tried with hyperventilation (HV). The oximeter was checked again after the descent. Throughout the flight, oximeter readings were taken at 1-minute intervals and continuous records of volume and frequency of breathing were made. Alveolar samples were taken frequently and analyzed in the chamber for CO_2 by the Scholander technique. Other samples were taken at the end of each period for analysis afterwards on the Haldane gas analysis apparatus.

Respiratory Circuit. Figure 1 is a diagram of the respiratory circuit and recording apparatus used in all ascents to test VPB. The subject wore a mask, designed for pressure-breathing which was equipped with a glass pipe-stem mouth-piece. The mouth-piece communicated via a side-tube in the mask inlet with a recording manometer, described below, which made it possible to obtain a record of the amount of pressure applied, duration of compres-

sion, and rate of respiration. During VPB the subject closed his lips about the mouth-piece inside the mask and exerted pressure against the manometer.

The main mask inlet communicated directly with a slide valve similar to one seen by one of us at the Mayo Aero-Medical Unit, for taking samples of alveolar air (fig. 1).

The air or oxygen supply was led through a Pioneer demand regulator and into a gasometer (commercial type). The latter was equipped with an electrical contact which was tripped once for each complete revolution of the registering lever. These contacts were recorded together with those of a time marker on a smoked drum outside the low pressure chamber. The gasometer

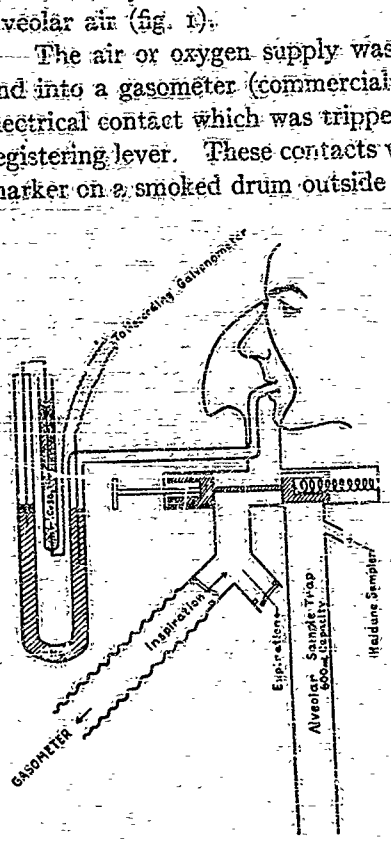

Fig. 1. Apparatus used for measuring the pressure developed in the lungs and for sampling the alveolar air.

lever made one revolution for approximately each 4.6 liters of gas which passed through. Inspired volumes were thus measured at ambient pressure and temperature, and were later corrected to 37°C., saturated, at ambient pressure, it being assumed that the gas supplied was dry initially. From the gasometer, the supply was led to the mask inlet through a brass Y which carried flap valves for separating the inspired and expired air, and then through the sampling valve mentioned above. The apparatus dead-space from Y-valves to subject measured about 225 ml., with some individual variation depending on mask fit. The resistance to breathing through the circuit amounted to about −4 cm. water on inspiration and +1 cm. water on expiration, measured at the mask inlet at ground level. At altitude the resistance was considerably less. Tests were made before and during each experiment for possible leaks.

Recording Manometer. A float in the open arm of a U-tube mercury manometer carried a wire which dipped into a column of dilute copper sulphate solution (fig. 1). Leads from the wire and an electrode sealed into the bottom of the copper sulphate column were connected in series with a dry cell and an Esterline-Angus recording galvanometer.[2] The length of copper sulphate column in the electrical circuit varied as the float rose and fell with changes of pressure in the mercury manometer, thus causing changes in electrical resistance and in the galvanometer deflections.

Sampling of Alveolar Air. At the end of a normal expiration, the subject depressed the plunger of the slide valve (fig. 1) thus establishing communication between the mask inlet and sample trap and cutting himself off from the ordinary pathway of inspiration and expiration. He then made a forced expiration into the sample trap, which consisted of a 4-foot length of wide-bore rubber tubing with a capacity of 600 ml. After the forced expiration was completed, the plunger of the slide valve was released, and the subject was free to proceed with his breathing. He then released the clip on the side tube of the sampling trap and signalled to the operator outside the pressure chamber. The latter drew the sample into an evacuated sampling bottle over mercury. The tube connecting the sampling trap with the outlet on the tank wall was of only a few ml. capacity, and was washed out with alveolar air before the first sample was drawn. Sampling tubes of 80 ml. and 240 ml. capacity were used at 18,000 ft. and 42,000 ft., respectively. Check experiments showed that use of the larger tubes did not result in any dilution of the sample with tank air entering the lower end of the sampling trap. The samples were analyzed in duplicate for CO_2 (and for O_2 in 10 runs at 18,000 ft.) in an 11 ml. Haldane burette. For samples containing more than 30 per cent CO_2 (as was usual at 42,000 ft.) it was necessary to draw about 7.5 ml. of sample into the burette, measure its volume accurately, and then dilute it with a measured amount of air or nitrogen to make a total volume of 10 to 11 ml., before proceeding with the analysis. This procedure introduces extra possibilities of error in the analyses, but duplicate analyses were run routinely and checked to within 0.1 per cent CO_2, a degree of accuracy quite sufficient for the purposes of these experiments. (At 42,000 ft., a difference of 0.1% CO_2 in the analyses amounts to only 0.081 mm. Hg.)

RESULTS

VPB and HV at 18,000 and 42,000 feet (Series A)

The data from these experiments are summarized in table 1. The complete data will be found in tables 3 and 5 of our original report (3) which are not reproduced here. The general trend of these averages at 18,000 ft. is

[2] We are indebted to Dr. R. B. Dean for the design of this recording manometer.

TABLE 1. COMPARISON OF NORMAL BREATHING, N, VOLUNTARY PRESSURE BREATHING, VPB, AND HYPERVENTILATION, HV, AT ALTITUDE. AVERAGE VALUES

TYPE OF BREATHING	ALVEOLAR pCO_2	ALVEOLAR pO_2	ALVEOLAR R.Q.	HbO_2	VENTILATION
18,000 ft. (10 exper., 7 subjects)					
	mm. Hg	*mm. Hg*		*%*	*l/min.*
N	32.8	34.9	[illegible]	81.7	14.0
VPB	24.0	51.7	1.10	85.8	22.7
N	28.1	30.6	.82	62.1	23.9
HV	18.9	51.7	1.08	91.9	26.9
18,000 ft. (19 exper., 10 subjects)					
N	30.7			78.0	16.6
VPB	26.6			83.0	22.5
HV	21.8			88.6	29.4
42,000 ft. (13 exper., 8 subjects)					
N	32.5	48.5[1]		81.2	16.1
VPB	31.4	65.8		89.5	22.8
HV	20.9	66.1		91.0	28.7

[1] Obtained by subtraction = (B 47 − pCO_2).

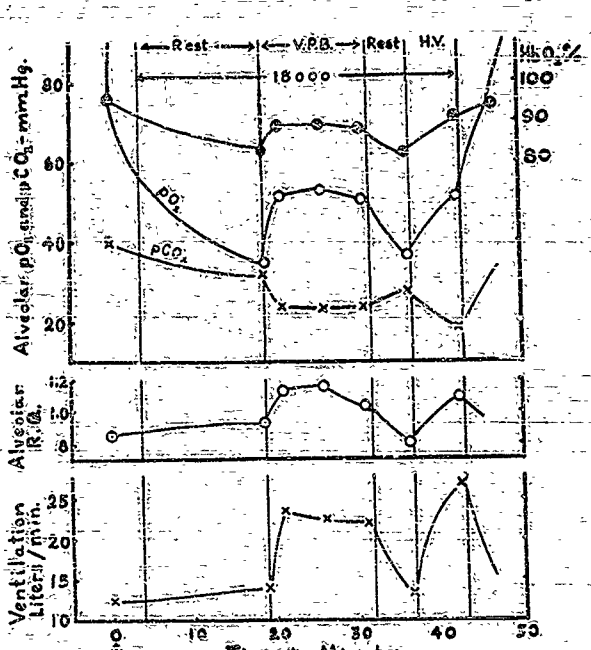

Fig. 2. AVERAGE VALUES OBTAINED in simulated flights to 18,000 ft. breathing air through a gasometer and gas mask and using voluntary pressure breathing and hyperventilation without pressure in alternation with normal breathing.

shown in figure 2 which illustrates the way in which the various quantities varied with time in the course of an experiment. In 10 of the 29 experiments no measurements were made of alveolar pO_2 and these were averaged in table 1 separately from the other 10 experiments. Three successive samples were taken during VPB but only one during HV. The 3 VPB samples agreed very closely and are averaged together. It is evident that pCO_2 is low and pO_2, ventilation, percentage saturation and R.Q. are all high compared to the normal, during both VPB and HV. The rise in the percentage saturation confirms the findings of Commoner (1) and all other workers in this field. This table shows in addition that there is very little difference between VPB and HV in any of the quantities measured. The agreement of course depends upon the proper adjustment of the ventilation rates obtained in the two cases. On the whole, in HV the pCO_2 was somewhat lower and the ventilation and saturation somewhat higher than in VPB.

The relation between hyperventilation and VPB is shown in figure 3 in which the change in alveolar pO_2 is plotted against the change in pCO_2 which resulted from the procedure employed. The 10 experiments here illustrated are those at 18,000 ft. in which analyses were made for both O_2 and CO_2, so that the values are quite independent of one another. The two sets of points for hyperventilation (crosses) and VPB (circles) have been fitted by regression lines by the method of least squares. The two lines have nearly identical slopes, these being a measure of the gain in pO_2 brought about by the lowering of the pCO_2. The vertical distance between the two lines represents the gain in pO_2 which resulted from the application of pressure provided the ventilation rate was maintained at such a level that the mean pCO_2 remained unchanged. In order to do this, the ventilation rate must be a little larger with VPB than in VH without pressure and the pCO_2 in the lungs during expiration, i.e., when the pressure is released, must be a little lower to compensate for the increase in pCO_2 which occurs, when pressure is applied. Evidently for most of the points, the gain in pO_2 due to the application of pressure is small compared to the total gain. The actual magnitude of this gain due to pressure is about 5.5 mm. Hg of O_2 tension (at a given pCO_2). Considering the scatter of points this does not differ significantly from the gain to be expected from the mean pressure of 21.7 mm. which was applied, the theoretical value being 21.7×0.209 or 4.5 mm. Hg.[3]

A similar curve can be plotted for the data at 42,600 ft. but in this case the pO_2 values were merely calculated from the pCO_2 values by difference since there were no other gases present. All the hyperventilation points, therefore, necessarily fall along a single straight line with a slope of 45° and the VPB

[3] The basis for this calculation is explained further below. The fraction of oxygen in the inspired air is 0.209. The mean pressure of 21.7 mm. was calculated from the average peak pressure of 54.3 mm. on the assumption that it was applied for 2 seconds out of 5 or 0.4 of the time.

points deviate from this line at corresponding pCO_2 values only in proportion to the mean applied pulmonary pressure which varied around the average value of 16 mm. (range 3–26 mm.).

This average pressure developed in the VPB technique at 42,000 ft. is slightly less than the average pressure developed at 18,000 feet (29 exper.) which was 19.6 mm. (range 9–30 mm.). This difference is due to the lower ambient pressure at altitude which permits a greater diminution in volume for a given applied pressure. In carrying out the VPB maneuver at altitude it is noticeable that the chest collapses more when pressure is applied than it does at ground level. Rahn *et al.* (2) have calculated the magnitude of this collapse and have shown that with smaller chest volumes there is a progressive decrease in the magnitude of the maximum expiratory pressure which can be developed.

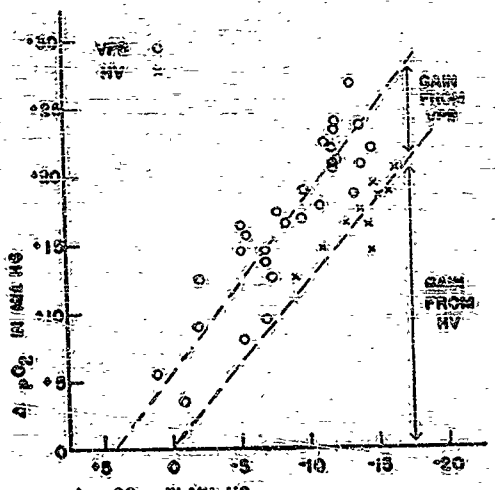

Fig. 3. Summary of 10 experiments simulated flights to 18,000 ft. in which a comparison was made between VPB (circles) and hyperventilation (crosses). The changes in alveolar oxygen tension thus produced (compared to the normal) are plotted against the corresponding changes in alveolar CO_2 tension. All values during VPB have been corrected for the pressure which was applied so that the figures plotted represent the actual mean increment in partial pressure of the gas.

In theory, VPB should be far more effective in raising the alveolar pO_2 when pure O_2 is breathed, as at 42,000 ft. because under such conditions all of the pressure is divided between pCO_2 and pO_2. From the data in table 1 for 42,000 ft. it can be calculated that the sum of pO_2 and pCO_2 increases 16 mm. above normal when VPB is used. At 18,000 ft. on the other hand, the added pulmonary pressure is divided between pO_2, pCO_2, and pN_2 in proportion to their several values. Unfortunately the N_2 has a concentration of around 80 per cent so that only 20 per cent of the pressure is left to divide between pO_2 and pCO_2. Thus from the data for 10 experiments at 18,000 feet in table 1 it can be calculated that the sum of pO_2 and pCO_2 increases in VPB by 8 mm. above the normal. This is greater than 20 per cent of the applied pressure of 21.7 mm. which is only 4.3 mm. The difference is due to the dilution of nitrogen at high R.Q. values which we have discussed elsewhere (9).

This high R.Q. in turn is due to the hyperventilation which accompanies VPB. The same amount of hyperventilation at 42,000 ft. is less effective in raising the pO_2 because of the absence of nitrogen in the inspired air. The increased ventilation of the VPB tends therefore to obscure the greater theoretical effectiveness of this procedure at oxygen-breathing as compared to air-breathing altitudes.

From the figures for 18,000 ft. in table 1 it can be seen that VPB provides no greater alveolar pO_2 than does HV but it does give a pCO_2 which is greater by 5.1 mm. At 42,000 ft. both pO_2 and pCO_2 are higher with VPB than with HV. At this level it is interesting to note that in comparison to the normal, VPB causes almost no change in the pCO_2 but is all applied to an increase of 17.3 mm. in the pO_2. In this connection it may appear strange that the ventilation at 42,000 ft. increases with VPB from a normal of 16.1 to 22.8 l/min. while the pCO_2 shows almost no change. It should be remembered that the ventilation is measured at ambient pressure while the pCO_2 and pO_2 values are corrected for the mean pressure in the lungs which is voluntarily elevated by the subject. Because of this applied pressure the actual mean pCO_2 in the alveoli does not fall in spite of the increased ventilation. In addition the metabolic rate has been increased some 45 per cent as will be shown below.

VPB and HV at 25,000 feet (Series B)

For practical purposes it is more important to test any emergency breathing procedure at an altitude of 25,000 ft. where only a few persons are able to maintain consciousness without special instructions. Any benefit of VPB or HV may therefore be expected to become evident in terms of better survival. The experiments at 25,000 ft. were very similar to those of Series A except that we did not usually test both VPB and HV in the same flight. It will be convenient, therefore, to report the HV and the VPB flights separately.

The apparatus was very similar to that described in figure 1 except that the gasometer was placed in the output rather than the intake side of the mask and the expired air was sampled beyond the gasometer and analyzed continuously by passing it through a Pauling oxygen tensimeter and a Cambridge Instrument Company carbon dioxide meter (thermal conductivity). Respiratory rates were recorded by means of an electrical contact activated by inspiratory and expiratory mask pressures. These contacts together with those made by the revolutions of the gasometer were recorded outside the chamber by pens writing on a moving paper strip. Not all of these measurements were made in all experiments.

Hyperventilation with Air. Instructions to our subjects before ascent were simply to 'hyperventilate, but not excessively' after they were shunted from oxygen to air at an altitude of 25,000 ft. The control of the rate and depth of breathing was left entirely to their own judgment. During this performance

they were required to write more or less continuously in order to provide reliable criteria of their performance. When subjects showed signs of failing they were encouraged by commands from observers to maintain their breathing. In cases of lack of response to questions, illegible handwriting or convulsive breathing, subjects were returned to oxygen where they immediately recovered. Such flights are designated as 'unsuccessful'. In a 'successful' flight the subject was able to maintain normal responses and handwriting for a period of 17 to 35 minutes.

In the hyperventilation series two types of runs were made. 1) Only oximeter and handwriting records were required. This effort to eliminate all other instrumentation was made in order to reduce breathing resistance to a minimum. This includes flights nos. 208 to 277 inclusive. 2) A full set of recordings was accomplished. It should be borne in mind that this equipment caused a greater resistance to breathing then would normally occur. This resistance was produced primarily by the special slide valve for sampling alveolar gases, the gasometer, and the relatively long pieces of tubing.

Of the 14 subjects engaging in these flights 8 succeeded while 6 failed. Three of the successful subjects repeated the run at another time sucessfully. Three of the unsuccessful subjects repeated the run one to three times and failed in all attempts. Altogether we have observations on 11 successful runs and 12 unsuccessful runs. The unsuccessful runs lasted on the average 6 minutes (range 4–15). The successful flights were terminated on the average in 28 minutes (range 17–35), but in each instance the subject wanted to continue and was considered in 'good' shape by his observers. These subjects all "felt as if they could have gone on forever."

A comparison of the successful and the unsuccessful flights is given in table 2. The data are more fragmentary in the unsuccessful flights which were terminated early and it is difficult to be certain of the cause of failure in all cases. On the average however it may be seen that the ventilation was slightly greater in the successful flights, being in all cases over 30 l/min. In at least 6 of the unsuccessful flights the ventilation was below 30. Likewise on the average in the successful flights the alveolar pCO_2 was lower both before and during the hyperventilation than in the flights that failed. This suggests that hyperventilation was at least one of the predisposing causes although there are some individual exceptions. In the unsuccessful flights the oximeter reading was always falling at the time the experiment was terminated and would presumably have gone lower than the last recorded figure if oxygen had not been supplied.

It is probably significant that those who failed did so repeatedly while those who were successful were likewise able to repeat their performance at will. It is not unlikely therefore that those who failed did so because of some special sensitivity to anoxia or acapnia rather than any inability to carry out

the technique properly. As indicated in table 5 about 50 per cent of all subjects are unable to retain consciousness at 25,000 feet by any type of breathing.

A graphical summary of the time course of the respiratory data from the successful flights to 25,000 feet with hyperventilation is shown in figure 4. It will be seen that the minute volume was about 30 l/min. and the arterial

TABLE 2. COMPARISON OF SUCCESSFUL AND UNSUCCESSFUL FLIGHTS ON HYPERVENTILATION AT 25,000 FEET

	SUCCESSFUL FLIGHTS	UNSUCCESSFUL FLIGHTS
Ventilation on O_2 before HV-l/min.	15	15
Ventilation on air-HV-l/min.	32.5 ± 4.6 (123)	30 ± 8.8 (29)
Duration of flight-min.	17–35 (+)	4–15
Terminal saturation-HbO_2 %	85 ± 4 (77)	77 ± 5 (12)
Alveolar pCO_2 before HV mm. Hg.	33.3	37.5
Alveolar pCO_2 during HV mm. Hg	19.6 ± 3 (15)	26.2 (2)
Alveolar pCO_2 during HV mm. Hg	31.7 ± 2.0 (13)	30.0 (1)
Number of subjects	8	6
Number of flights	11	12

Figures in ( ) indicate number of figures averaged. Standard deviations are given where possible.

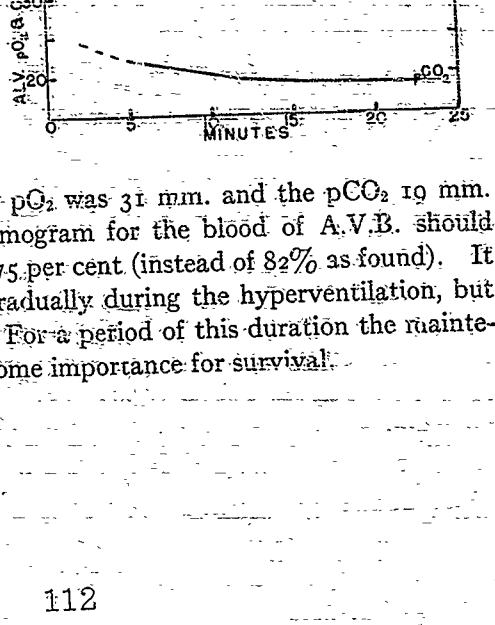

Fig. 4. AVERAGE VALUES OBTAINED in successful flights using hyperventilation on air at 25,000 ft. plotted against time measured from the beginning of the exposure. Each point is the average of 6 to 11 experiments and subjects. The same experiments and subjects are not represented in the figures for all the quantities plotted. Minute volumes in liters B.T.P.S. Hemoglobin saturations are based on analyses of alveolar air by the Haldane method in 3 experiments.

saturation above 80 per cent. The pO_2 was 31 mm. and the pCO_2 19 mm. which according to Henderson's nomogram for the blood of A.V.B. should give an arterial saturation of about 75 per cent (instead of 82% as found). It is noteworthy that the R.Q. falls gradually during the hyperventilation, but remains above 1.0 for 24 minutes. For a period of this duration the maintenance of a high R.Q. is a factor of some importance for survival.

Voluntary Pressure Breathing with Air. The technique of this procedure was essentially the same as in our previous experiments except that greater pressure was applied by the abdominal muscles and less by the thoracic muscles and there was a greater inflation of the chest and a greater ventilation. These changes resulted from a visit from Dr. Commoner who endeavored to coach our subjects in his particular technique. The pressure was exerted against a mercury manometer through a pipe stem held in the mouth and was maintained (when possible) for 2 out of 5 seconds. Seven subjects attempted this procedure and three were successful, in maintaining consciousness for 17 to

TABLE 3. VOLUNTARY PRESSURE BREATHING AT 25,000 FEET

FLIGHT NO.	TIME ON AIR	MEAN PULM. PRES.	HbO_2	VENT.	EXPIRED CO_2	EXPIRED O_2	CO_2 OUTPUT	O_2 INTAKE	EXPIRED R.Q.	ALVEOLAR AIR		
										pCO_2	pO_2	K.Q.
Successful Flights												
	min.	*mm. Hg*	%	*l/min.*	%	%	*cc/min.*			*mm. Hg*		
323	5	20	94							22.0	34.2	1.20
	15		99	38.1	7.92	14.19	657	532	1.23			
	20	12	90	48.6	7.57	13.32	803	774	1.04	22.0	33.1	1.25
	30	12	90	34.9	7.19	14.81	545	443	1.23	22.0	30.8	1.07
325	6	10[1]	85	25.7	7.50	15.64	420	260	1.61	23.6	35.2	1.69
	12–19	12[1]	77–82	31.2	7.26	14.99	494	440	1.12	22.4	33.4	1.30
	25–30	20	83	28.9	7.06	13.75	445	456	.99		33.0	
328	5–8	7[1]	82–77	28.0	6.04	16.23	368	254	1.45	24.2	27.5	1.06
	16	10[1]	77	55.1	7.65	16.67	845	411	2.05		31.8	
	25–29	10	78	61.0	7.50	15.99	1000	560	1.78	22.3	26.4	0.88
Averages		12	84	39.0	7.23	15.07	620	458	1.39	22.6	31.7	1.21
Miscellaneous Flights												
324[2]	5	20	69	48.2	4.65	15.63	489	565	0.87	21.2		
327[3]	9 (+27)	30	71		5.54	15.0	474	515	0.92	20.6	30.7	0.80
322[3]	5 (+30)	30	85	39.5						20.0	29.3	0.72

[1] Approximate values. [2] Unsuccesful flight. [3] VPB at end of hyperventilation flight.

35 minutes. It is of some interest that only those succeeded who were also successful with straight hyperventilation. Of the 4 failures in this group 2 succeeded with hyperventilation while the other 2 did not. It is difficult to say to what the failures were due. At the beginning of VPB all our subjects developed a peak pressure of about 100 mm. In the unsuccessful flights a fairly good mean pressure was recorded because the subjects had to give up VPB and take oxygen before they had time to tire of the procedure. Of the 3 successful subjects one held his pressure faithfully for 2 seconds but the pressure so maintained was not very high; one developed a higher peak pressure but was unable to maintain it for 2 seconds; and the third was able to exert a

pressure only once every fourth breath so that the mean pressure was low. The ventilation was perhaps a little lower in the unsuccessful flights (28 as compared to 30.2 l/min.) and the percentage saturation just before collapse was 70 per cent as compared to 85 per cent in the successful flights. It appeared that the severe anoxia at 25,000 ft. weakened the determination to continue the development of pressure and made the VPB procedure more difficult than it seemed to be at 18,000 feet.

Detailed data for the three successful VPB flights at 25,000 ft. are given in table 2 together with data from one unsuccessful flight and two flights in which VPB was tried after 30 minutes of H.V.

The most significant fact about this table is the low pCO_2 value of 22.6 mm. Hg in the alveolar air and the high R.Q. of 1.39 due to the overventilation. Thus an average arterial saturation of 84 per cent was recorded in spite of the low pO_2 of 31.7 mm. in the alveolar air. The figures for the oxygen consumption will be referred to later.

An altitude of 25,000 ft. is a critical one for survival since only 50 per cent of all subjects are able to maintain consciousness (table 5). Hence, the value of 31.7 mm. for the pO_2 in the alveoli in the successful subjects supports the idea that 30 mm. is approximately the irreducible minimum for conscious survival.

Increased Oxygen Consumption Due to VPB

It seems obvious that the strenuous effort required for the VPB procedure will considerably increase the need for oxygen. There is danger therefore that any increase in the alveolar oxygen tension which may result from the pressure applied will be more than offset by the increased amount of oxygen which must be driven into the blood and tissues. To investigate this question we made use of the Sanborn metabolism machine in some experiments at ground level. The subject wore a mask which could be connected by a 3-way stopcock either to the room air or to the apparatus. In the Sanborn apparatus the gases are circulated by a fan but to avoid all possibility of rebreathing expired air it was necessary to insert inspiratory and expiratory valves between the stopcock and the spirometer circuit. The experiment began with the subject sitting at rest for 5 to 10 minutes breathing through the mask to room air. Then the stopcock was turned to the spirometer and a record was taken for 8 minutes, for the determination of the resting rate of oxygen consumption. At the close of this record VPB was started and 4 minutes later another 6-minute record was taken. The purpose of the 4-minute wait was to avoid any false oxygen uptake due to increased pO_2 in the lungs (as a result of hyperventilation) or due to increased mean saturation of the blood with oxygen (Bohr effect at lowered pCO_2). Previous experiments (unpublished) had shown that after 4 minutes this false intake (amounting to some 40 cc.) was largely

complete and the rate of oxygen consumption had returned approximately to its true metabolic level.

Records were obtained with this technique on 12 subjects: (11 male, and 1 female), all of whom had been used in VPB ascents. The results are conclusive and confirm our supposition that the oxygen uptake increases considerably during VPB, due to the work involved. The data are summarized in table 4, which gives the individual results and averages for the group. Here it is seen that VPB at an average maximum pressure of 51.8 mm. Hg increases the oxygen consumption 45.5 per cent over rest, on the average. All subjects showed an increase, ranging from 20.7 per cent to 91.0 per cent. This experiment also shows that at a rate of 10.9 breaths/min. the subject, although

TABLE 4. EFFECT OF VPB ON RATE OF OXYGEN CONSUMPTION

SUBJECT	REST			VPB				INCREASE IN O_2 USED
	O_2 used	RATE /MIN.	VENTILATION	O_2 USED	RATE /MIN.	VENTILATION	PEAK PRESSURE	
	ml/min.		*l/min.*	*ml/min.*		*l/min.*	*mm. Hg*	%
1	310	14	14.8	530	14	20.0	65	70.9
2	260	12	9.7	380	13	21.4	50	46.1
3	295	11	8.0	430	13	28.9	60	45.7
4	290	14	12.1	390	13	12.1	50	34.5
5	260	13	7.4	390	10	22.7	52	50.0
6	220	11	10.2	420	10	22.7	52	91.0
7	300	14	10.3	410	12	19.4	48	36.6
8	285	18	11.2	480	12	15.9	65	68.5
9	290	17	8.7	370	9	15.1	45	27.6
10	240	10	6.2	290	10	10.3	47	20.8
11	370	15	8.1	495	7	9.8	45	33.8
12	290	15	8.9	350	8	13.3	45	20.7
Average	285	13.7	9.6	415	10.9	16.4	51.8	45.5

he was instructed not to increase his minute volume, will on the average do so by 6.8 liters. The same amount of voluntary hyperventilation without pressure would require an increase in oxygen consumption of only 7.1 cc/min. (16), or 3 per cent of the resting value. Therefore, it can be said that the application of pressure, chiefly by the abdominal muscles, was responsible for 93.5 per cent of the increase in oxygen uptake that took place in these experiments.

In table 3 some figures are given for the rates of oxygen consumption and CO_2 output during VPB at 25,000 ft. These values were calculated from the percentage composition of the expired air and the ventilation rates in l/min. The average rate of oxygen consumption in these 3 experiments was 458 cc/min. which is about 50 per cent higher than a normal rate of 300 cc/min. for a resting man. Since there were no resting values on these same subjects,

however, this can hardly be regarded as a rigorous confirmation of our ground level determinations.

Further confirmation of these results may be obtained by calculating the rates of oxygen consumption from the alveolar air data of table 1 of the 25,000-ft. flights using the alveolar air equation (9). The results show a 31 per cent increase due to VPB and a 23 per cent increase due to HV. These figures, however, may be partially explained by an increase in the dead space which was assumed to have a constant value of 360 cc. Because of this uncertainty the results are not presented in detail.

One further confirmation of the importance of the increased rate of oxygen consumption in VPB as compared to HV is shown in the graphs from *subject C.G.B.* in flight 327 which are shown in figure 5. In this experiment the subject started at 25,000 ft. with the VPB procedure and was able to maintain a good mean pulmonary pressure but the minute volume fell so low that he collapsed in 10 minutes from desaturation of the blood and resulting anoxia, with an expired pO_2 less than 30 mm. After a short recovery period on oxygen the subject began to hyperventilate on air and continued this successfully for 29 minutes with a satisfactorily high oxygen tension of 37 mm. in the expired air and an arterial saturation of 87 per cent as indicated by the ear oximeter. At the end of this period of HV the subject again began VPB with the result that his arterial saturation and the pO_2 of his expired air decreased markedly without much change in his minute ventilation volume. This occurred in spite of the increased pulmonary pressure and can only have been due to the increased utilization of oxygen. The temporary increase in the arterial saturation was due to the increased pulmonary pressure acting before the rate of oxygen consumption had increased to its new level. If the rate of oxygen

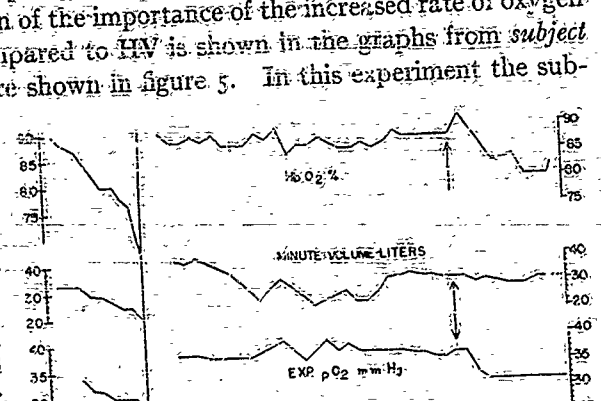

Fig. 5. Data of flight 327 in which subject *C.G.B.* tested VPB and voluntary hyperventilation (VHV) at 25,000 ft. A recovery period on oxygen intervened between the first period on VPB and the period on VHV. See text.

consumption is calculated from the oxygen content of the expired air and the ventilation volume it is found that the rate was 463 cc/min. during HV and 589 cc/min. during VPB. If we assume arbitrarily that HV required a 15 per cent increase over normal then the figure for VPB represents a 46 per cent increase which is in good agreement with our other values.

In a previous (unpublished) report we have shown that the elastic work of breathing is given by the expression $W = \frac{fKT^2}{2} \times 10^{-5}$ where f is the number of breaths per minute, T is the tidal volume in cc., K is the slope of the relaxation pressure curve, $\frac{dp}{dT}$ (p is measured in cm. H_2O) and W is the work per minute in kg. m. Using this formula and a value of K = 0.01 it can be calculated that the elastic work of breathing is 0.34 kg. m. per min. for normal breathing at rest and 2.9 for hyperventilation at a frequency of 12/min. and a volume of 22.8 l/min. If at the same time the subject stops at each inspiration with a total lung volume of 4000 cc. and develops a pressure of 52 mm. Hg or 70 cm. H_2O the potential energy stored in this compressed air amounts to $\frac{52}{(760-47)} \times 4000 \times \frac{70}{2} \times 12 = 1.22$ kg. m/min. This represents a 41 per cent increase in the work performed. In this estimate the work of moving the air against viscous resistance and turbulence has not been considered but this would not increase the work without pressure development more than perhaps 20 per cent (unpublished data). If this extra work of VPB is done with 5 per cent efficiency like the normal respiration (11) then it should require an extra 11.5 cc. O_2/min. which is the approximate energy equivalent of $\frac{100}{5} \times 1.22$ kg. m. Since the extra oxygen actually used was more than 10 times this amount it is evident that the efficiency of the actual work done in VPB is exceedingly small. Presumably the effort represents a nearly maximal isometric contraction of all the muscles of the trunk exerting pressure against one another. It must be regarded, therefore, as a rather expensive compensatory mechanism. It might be noted that the above calculation is for VPB at ground level. At altitudes the work of developing pressure becomes greater because the lung volume is more compressed when pressure is applied. On the other hand, the work against turbulence in moving the air is less as the density of the air diminishes.

DISCUSSION

The theoretical interpretation of the results which we have obtained in these experiments is best illustrated by means of pO_2–pCO_2 charts. The theory

of these charts has been discussed at some length by Fenn *et al.* (9). Such a chart is shown in figure 6 for the case where pure oxygen is breathed at 42,000 ft. At ambient pressure the alveolar air composition must be represented by a point on the 42,000-ft. diagonal for the equation of this diagonal is $pO_2 + pCO_2 = B\text{-}47 = 81$ mm. Hg. The point N on this diagonal represents the alveolar air breathing oxygen before HV or VPB, the pCO_2 being 33 mm. During hyperventilation without applied pressure the alveolar point moves down the altitude diagonal to H with a pCO_2 of 21 mm. and the arterial saturation increases from 86 to 94 per cent as indicated by the family of curved lines. When VPB is tried at this altitude the alveolar point moves up and to the right in such a way that both pCO_2 and pO_2 increase in proportion to $(B\text{-}47 + p)$ where p is the mean pressure applied as indicated by the first arrow. At this point the ventilation increases and brings the pCO_2 back to nearly its original value of 32 mm. with a saturation of 94 per cent instead of 86 per cent. The

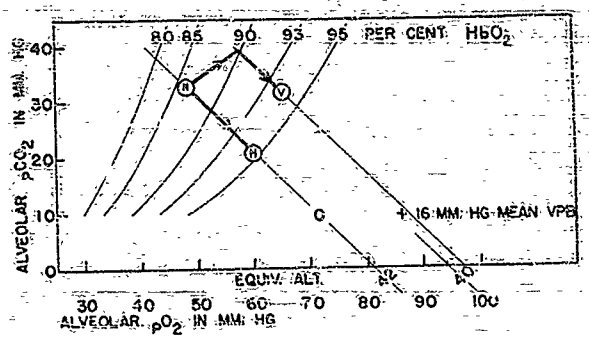

Fig. 6. DIAGRAM OF CHANGES in alveolar air composition during normal breathing (N), hyperventilation (H) and voluntary pressure breathing (V) at 42,000 ft. breathing oxygen. Ordinates and abscissae are alveolar tensions of CO_2 and O_2 respectively. Diagonal lines represent altitudes and curves are iso-saturation lines. See text.

final position is represented by point V on the diagonal corresponding to an altitude of about 39,400 ft.[4]

A similar chart for 18,000 ft. is shown in figure 7. The alveolar point breathing air at 18,000 ft. before VPB is indicated by point N_1. As we have shown elsewhere (9) when nitrogen is present in the breathing mixture each altitude is represented not by a single diagonal but by a family of diagonals radiating from the same pO_2 value on the X axis, the slope depending upon the R.Q. Three such diagonals for 0.82, 0.94, and 1.08 are shown for 18,000 ft. and N_1 is located on the diagonal for 0.94. When VPB starts the tensions of both O_2 and CO_2 are increased in the proportion of $(334 + 19.6)/334$ as indicated by the short line up and to the right from N_1. This is much less than the corresponding movement at 42,000 ft. because the ambient pressure is so much greater. The increase in ventilation then moves the alveolar point

[4] The reader who is unfamiliar with this chart will find it helpful to note that the position of the alveolar point on a given altitude diagonal depends only on the alveolar ventilation and the metabolic rate. At an infinite ventilation volume or a metabolic rate of zero the alveolar point is still on the same altitude diagonal but at its point of intersection with the X axis where $pCO_2 = 0$.

to point V which is on the R.Q. = 1.15 diagonal corresponding to an altitude of about 17 000 ft. In this case the alveolar point does not simply move down one diagonal but the increased R.Q. moves it also to the right to a new diagonal. The point N_2 corresponds to the alveolar air during normal breathing on air after VPB and before HV begins (table 1). N_2 is below N_1 because CO_2 is still being retained; i.e., the subject has not yet recovered from the CO_2 blown off during the VPB. The R.Q. is therefore only 0.82 instead of 0.94. When hyperventilation begins CO_2 is blown off and the R.Q. moves to point H on the 1.08 R.Q. diagonal for 18,000 ft. Comparing points H and V, it is evident that the percentage saturation is a little better at H but both pO_2 and pCO_2 are lower so that the performance is probably not quite so good as at V.

At this point it might be noted that in our 18,000-ft. experiments the effects of HV were compared after VPB when some of the preformed CO_2 had

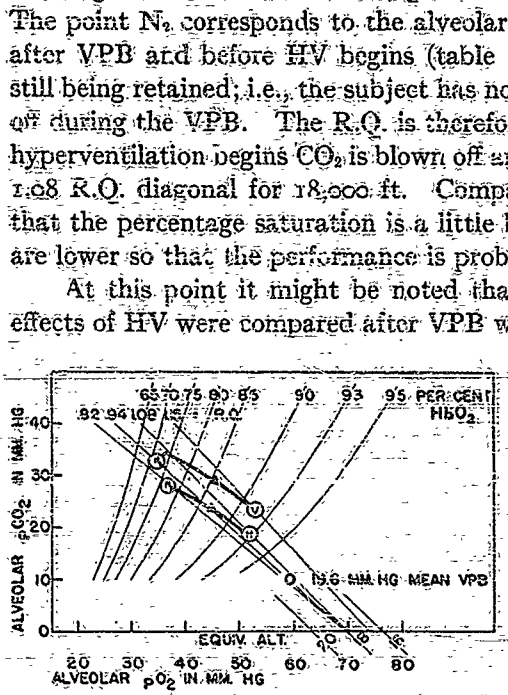

Fig. 7. Diagram of changes in alveolar air composition during normal breathing (N_1 and N_2), hyperventilation (H) and voluntary pressure-breathing (V) at 18,000 ft. breathing air. Ordinates and abscissae are alveolar tensions of CO_2 and O_2 respectively. See text.

been blown off and the increase in pO_2 due to this high R.Q. effect was less than normal. The results would presumably have been more favorable to HV if it had been tried before VPB instead of after. Likewise it should be pointed out that because of this R.Q. effect on the pO_2 the simple process of hyperventilation is more useful at 25,000 ft. than at 42,000 ft. When pure oxygen is used there is no such R.Q. effect to assist the subject.

The same pO_2-pCO_2 chart can be used in figure 8 to summarize the situation of a man trying to survive at 25,000 feet with VPB. The normal composition of the alveolar air at a series of increasing altitudes is represented by a broken line which bends down when the pO_2 falls below 50 mm. This bending is due to the hyperventilation which normally occurs with anoxia. If, however, the ventilation were not increased and the R.Q. retained its normal value of 0.8 the alveolar point would be represented by point 1 on the R.Q. = 0.8 diagonal for 25,000 ft. At this point the pO_2 would be only 6 mm. and collapse from anoxia would be inevitable. If at point 1 however the alveolar ventilation were to increase (without change in R.Q.) from a normal value of 7.7 l/min. to 14 l/min. the alveolar point would move down the 0.8 diagonal

to point 2 where the pCO_2 is 20.9 mm. (table 1) with an 18-mm. increase in pO_2. This lowering of the pCO_2 however results in a blowing off of preformed CO_2 which increases the R.Q. to 1.2. To keep the pCO_2 from increasing the ventilation is increased to 20 l/min. which brings the alveolar point to 3 on the $R.Q. = 1.2$ diagonal with a further increase of 7 mm. pO_2.

If in addition the subject is able to maintain a mean pressure in the lungs of 20 mm. (50 mm. peak pressure maintained 2 out of 5 seconds) he can add another 4 mm. ($\frac{1}{5}$ of the total since $\frac{4}{5}$ is applied to nitrogen) to either CO_2 or O_2. If the breathing remains the same this is added to CO_2 (point 5) but if the CO_2 is kept constant by a sufficient increase in ventilation then it can be added to O_2 and the alveolar point will move on the diagram from 3 to 4. The increase in ventilation needed to accomplish this last increment in pO_2 must be sufficient to cover an increase in metabolic rate of about 40 per cent as already

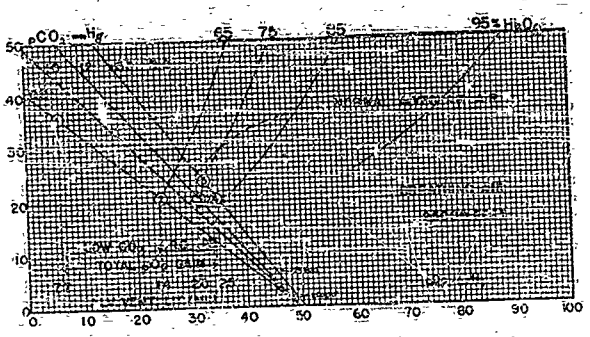

Fig. 8. Diagram of changes in alveolar air composition during voluntary pressure breathing at 25,000 ft. breathing air. Ordinates and abscissae are alveolar tensions of CO_2 and O_2 respectively. See text.

indicated. Either point 4 or 5[5] should be consistent with the maintenance of consciousness at 25,000 ft. for some persons because they both lie above a pCO_2 level of 20 mm. where acapnia is not serious and to the right of the dotted alveolar air line where some persons at least have been able to survive long enough to provide alveolar air samples.

This discussion has shown that a subject who remains conscious at 25,000 ft. due to VPB owes 4 mm. of his extra pO_2 to the pressure which he is applying and 25 mm. to the increase in ventilation over the normal value. The essential reason for his survival is therefore the extra ventilation rate which he maintains.

The work reported in this paper represents a contribution to the controversy which was aroused, particularly in Naval laboratories, following the publication of Commoner's report concerning the relative merits of voluntary pressure breathing and simple hyperventilation as a method for prolonging sur-

[5] Points 4 and 5 are represented somewhat arbitrarily as located on the R.Q. = 1.08 diagonal for an altitude of 24,600 feet. An infinite number of other combinations of R.Q. and altitude could be selected for this point. This particular R.Q. was calculated on the assumption that the metabolic CO_2 output would increase 40 per cent (like the O_2 intake) and the CO_2 blown off would remain the same. Point 5 is calculated on the doubtful assumption that the R.Q. would remain 1.08.

vival at 25,000 ft. in case of emergency. A summary of some of the findings is given in table 5. The general conclusion from this table is that both HV and VPB improve the chances for survival at 25,000 ft. On the basis chiefly of their tests under actual flight conditions Houston *et al.* (4) concluded that hyperventilation because of its relative simplicity was better than VPB as an emergency measure. On the whole, neither HV nor VPB permit more than about 50 per cent survival at 25,000 ft. The chief emphasis so far has been upon the application of VPB to survival at 25,000 ft. Actually it is more likely to be useful at altitudes above 40,000 ft. breathing pure oxygen for, under these conditions, all the pulmonary pressure can be applied to the oxygen and the increase in saturation may be considerable.

One of the points stressed by many observers has been the great effort involved in VPB which interferes with the performance of routine tasks and

TABLE 5. PERCENTAGE OF SUBJECTS REMAINING CONSCIOUS AT 25,000 FEET

	NORMAL		VPB		HV	
	%	*n*	%	*n*	%	*n*
Houston *et al.* (Rep. No. 3)	7	28	88	38	67	38
" " " plane			27	37	69	31
Houston *et al.* (Rep. No. 2)					48	40
Riley *et al.*, 1944					48	50
This report			43	7	57	14

The figures under *n* indicate the number of subjects involved in the experiments. All experiments were simulated flights in low pressure chambers except the actual flights in a plane carried out by Houston *et al.* in report No. 3.

fatigues the subject. The 45 per cent increased rate of oxygen consumption which we have measured indicates the magnitude of this effort. It is worth while to consider what this means in terms of diffusion gradients. In the lungs at a diffusion capacity of 60 cc/min. Hg/min., a 5-mm. gradient is sufficient for a resting rate of oxygen intake of 300 cc/min. If this is increased 45 per cent the gradient will also have to increase by a similar percentage so that a 3-mm. increase would be sufficient. This could easily be expected from a mean pulmonary pressure of 20 mm. if $\frac{1}{5}$ is applied to the oxygen. Considering the lungs alone an increase of a few mm. Hg pressure might be critical. The diffusion in the tissues must also be considered however. In the alveoli there is an oxygen pressure of 30 mm. of which 5 mm. is used in the lung. The mean pO_2 in the lung capillaries is therefore 25 mm. and the mean pressure in the tissue capillaries could hardly be much greater than 20 mm. If this 20 mm. is barely sufficient to supply the tissues at rest then to take care of a 45 per cent increase in oxygen intake there will have to be also an increase of 45 per cent in the diffusion pressure (or in the tissue diffusing capacity) or 9 mm. more of average oxygen tension in the tissue capillaries. It is hardly

reasonable to expect an increase of this amount in VPB and the increased work involved must be regarded as a definite disadvantage. It is, of course, true that the 45 per cent extra oxygen is used only in the muscles and the important point in an emergency is the maintenance of the oxygen supply of the brain. A few mm. Hg increase in oxygen pressure in the cerebral capillaries for a short time might permit survival until a better oxygen supply is available for the repayment of the oxygen debt incurred, meanwhile, by the muscles.

Our own recommendations for emergency survival would be to breathe a little more than twice as much air as normal; exert a little pressure without excessive effort during expiration if it can be done conveniently. This will be especially useful at oxygen-breathing altitudes. If symptoms of acapnia develop such as tingling in the fingers and toes the amount of breathing should be diminished slightly until this symptom is controlled.

SUMMARY

A study was made of the relative effectiveness of a voluntary increase in the pressure of gases in the lung at the height of each inspiration as a means of improving the tolerance to high altitudes in case of emergency. The increase in the saturation of the arterial blood which results from this voluntary breathing pressure breathing (VPB) recommended by Commoner is shown to depend chiefly upon the concomitant hyperventilation. Systematic comparisons were made at simulated altitudes of 18,000, 25,000, and 42,000 ft. of the relative effectiveness of voluntary pressure breathing and simple moderate amounts of hyperventilation. Simultaneous measurements were made of the composition of the alveolar air and the volume of the ventilation.

VPB is more effective at 42,000 ft. breathing oxygen than at 18,000 ft. breathing air because in the former case all of the pressure is applied to the oxygen and in the latter case 80 per cent is applied only to the nitrogen. Hyperventilation on the other hand, is more effective when breathing air because of the increased R.Q. and the resulting nitrogen dilution, or increased oxygen pressure which occurs. Measurements of the rate of oxygen consumption showed an increase of 45 per cent during VPB. This is a measure of the considerable effort required for the development of pressure and greatly diminishes the value of the procedure. Experiments at 25,000 ft. show that an alveolar oxygen tension of 30 mm. is close to the minimal pressure consistent with maintenance of consciousness. Only about 50 per cent of all normal male subjects can maintain consciousness at 25,000 ft. with either voluntary pressure breathing or hyperventilation.

Since hyperventilation is much easier and equally as effective as the arduous voluntary pressure breathing procedure it is recommended for emergency use. The degree of hyperventilation should be a little more than twice the normal and should be diminished if any signs of acapnia appear.

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PRESSURE BREATHING

by

Wallace O. Fenn

Summary of a talk given at a conference held at the
Aero-Medical Laboratory at Wright Field
October 16, 1945

At the request of the Committee on Medical Research of the O.S.R.D. I have recently had the privilege of cooperating with Drs. A. L. Barach, E. B. Ferris, and C. F. Schmidt in the preparation of a manuscript reviewing the physiological effects of pressure breathing (1). Since this manuscript will presumably be published in due time it is unnecessary in this article to do more than summarize briefly the results which have been obtained and to enlarge upon certain aspects of pressure breathing which were not perhaps as thoroughly discussed in our cooperative manuscript as they might have been.

Most of the statements and conclusions mentioned in this article are supported by evidence from all the laboratories working on pressure breathing. It is impossible in this brief summary to give full credit to all concerned and the reader must therefore be referred to the other manuscript for fuller literature citations.

Men have breathed at pressures varying all the way from a little over one tenth of an atmosphere of O_2 to a little over ten atmospheres (of air) without suffering severe consequences. Large differences of pressure therefore are inocuous or even imperceptible provided they are uniformly distributed over the body. Differential pressures or pressures unevenly distributed always lead to uncomfortable or serious consequences. A pressure in the gut higher than that outside may become most distressing. If the finger is immersed in mercury the difference in pressure at the meniscus is quite perceptible but the uniform pressure over the remainder of the finger feels in no way abnormal. Likewise any appreciable difference in pressure between the inside and the outside of the chest in excess of a few cm. of water leads to important physiological consequences. Under normal conditions no such pressure differences occur because the resistance of the respiratory passages is low enough to transmit the necessary air at pressure gradients of 1 or 2 cm. At maximum rates of ventilation however and particularly during expiration the pressures may build up to 6 or more cm. of water, positive in expiration and negative in inspiration. Very high pressures are also of frequent occurrence in severe muscular effort and in straining movements such as those involved in defecation. The body is accustomed to transient pressure peaks of this sort. They are not dangerous because they are produced by voluntary compression of the thorax which therefore does not expand with the pressure which is applied. The added pressure is therefore supported by the chest wall not by the delicate lungs themselves. The application of pressure from the outside however for purposes of

supercharging the pilot with oxygen, as in aviation, is a much more serious physiological problem chiefly because the application is continuous rather than transient and the chest is enlarged. The subject of pressure breathing concerns then the artificial elevation of the lung pressure for purpose of raising the oxygen tension and the physiological responses of the body to this unusual situation.

The mechanical aspects of pressure breathing are illustrated in Fig. 1, the data for which were obtained largely under the direction of Dr. Rahn (C.A.M. Nos. 111 and 430). The curves P_e and P_i represent respectively the maximum expiratory and inspiratory pressures that can be exerted by voluntary effort at different lung volumes. The dotted curve P_r represents the relaxation pressures of the chest at different lung volumes. The right side of the diagram represents the area of positive pressure breathing and the left side covers all situations in which the pressure in the chest is negative relative to the pressure over the rest of the body. When positive pressure is applied to the lungs the chest tends to be inflated along the curve P_r and this curve is therefore a measure of all the passive forces which resist inflation including lung elasticity and the rigidity of the chest wall. When the chest is inflated the rise of pressure in the veins is about half the rise of pressure in the lungs. Our findings in this respect are in agreement with those of Barach, Ferris and others. Dr. Otis in our laboratory has used this difference between venous and pulmonary pressure as a measure of lung elasticity and has developed some interesting diagrams which permit the prediction of the rise in venous pressure for different pulmonary pressures and volumes. A corollary of this theory is that if inflation of the chest is prevented any rise in pulmonary pressure results in an equal rise in venous pressure. This is confirmed by figures which Dr. Otis has obtained.

In collaboration with Drs. Cournand and Richards, Dr. Barach has shown that the rise in peripheral venous pressure is equal to the rise in right auricular pressure. This indicates that the pressure gradient from the periphery to the heart remains unchanged so that the venous inflow is not apparently diminished. Nevertheless in certain individuals and at certain pressures in all individuals, pressure breathing causes a reduction of cardiac output of 15 to 20%. This has been shown by the Roentgenkymograph, the ballistocardiograph and the direct Fick methos (Cournand and Richards). The cerebral circulation however probably remains unaffected because the arterial pressure is elevated to approximately the same degree as the intr- -oracic pressure. This was shown not only by our own measurements with the indirect method but much more elegantly by Dr. Barach with the use of the Hamilton manometer. The decrease in cardiac output must therefore be attributed to a diminished peripheral flow and vasoconstriction. As evidence of such a vasoconstriction we have found a decrease in the finger pulse and this has been confirmed by Bloom et al (4) with the impedance plethysmograph. A more direct measurement of blood flow through the fingers is obtained by the venous occlusion plethysmograph, which likewise shows a decrease with PB. In addition the finger temperature is found to be diminished temporarily at the onset of PB (Bateman and Sheard) (5).

Still further evidence of vasoconstriction is found if the leg is enclosed in a plethysmograph while the subject reclines on a tilt board (CAM No. 249). When

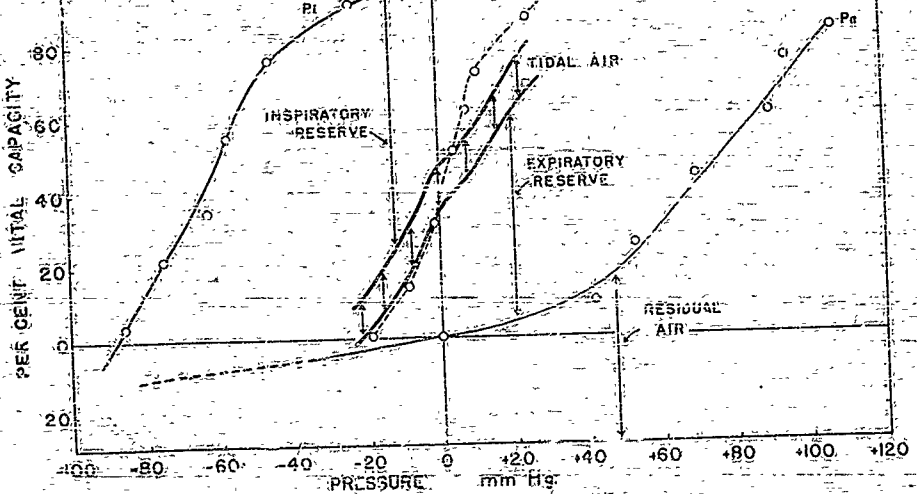

Figure 1

$$W = \frac{kfT^2}{2} + \frac{cr^2n^2}{30}$$

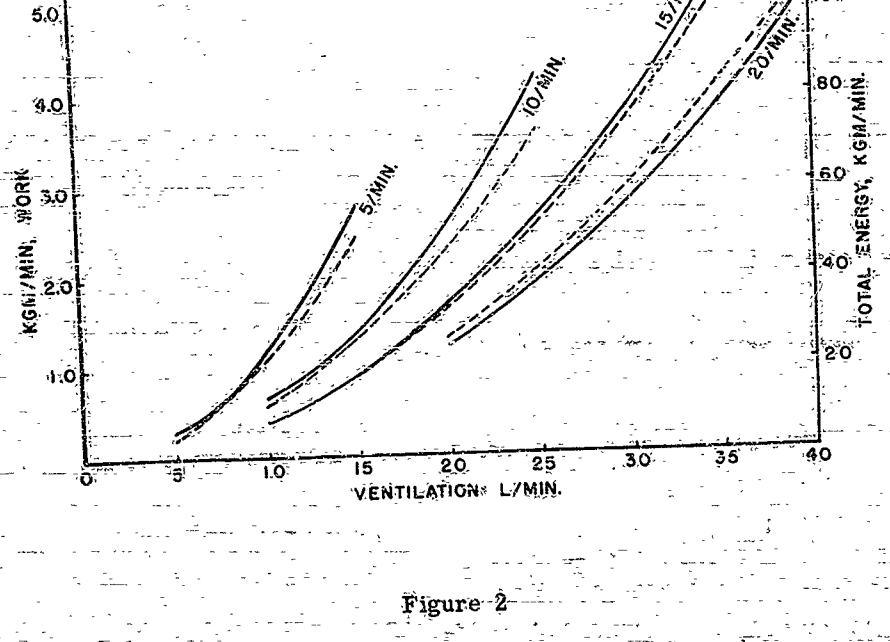

Figure 2

pressure breathing is applied the feet grow heavier and the leg increases in volume due to back pressure from the veins. The change in the balance of the tilt board was such that we had to assume that about 500 cc was displaced from the lungs due to the PB. The evidence from peripheral vasoconstriction comes from a modification of this experiment whereby the back pressure effects of the venous pressure are prevented by introducing a venous "dam" in the form of a pneumatic cuff around the leg above the plethysmograph. When this is inflated above the level of the venous pressure but below the arterial pressure the onset of PB results in a decrease rather than an increase in the volume of the leg. This effect is reversible and it can be repeated at will with great regularity. This may be taken as direct evidence of a vasoconstriction either in the arterioles or the veins. Without the pneumatic cuff the vasoconstriction is obscured by the passive inflation of the veins.

Breathing against a continuous pressure is more tiring than normal breathing because the work required is greater. The work of breathing can be estimated from the relaxation pressure of the lungs and chest. The relaxation pressure curve is the graph derived from plotting the pressure developed in the lungs when the muscles are completely relaxed against the corresponding volume of the lungs. If the chest is much inflated before the muscles are relaxed (with the nose occluded and a monometer tube in the mouth) the pressure is positive but if relaxation occurs after a maximal exhalation the pressure is negative. The area under a curve of this sort is the elastic work required to inflate the chest to various degrees. There is also some viscous work which can be approximately evaluated with the help of some simplifying assumptions and some data of Neergård and Wirz on the pressure gradients required for various rates of flow between the mask and the alveoli. The equation for the work of breathing per minute (W) is then

$$W = \frac{kfT^2}{2} + \frac{cf^2T^2}{30}$$

In this equation f is the frequency of breathing, d the dead space, T the tidal volume, c is a constant proportional to the resistance to air flow between mask and alveoli, and k is the slope of the relaxation pressure curve. The first term of the equation is the elastic work and the last term is the viscous work (C.A.M. No. 430). Calculating the work in this way Dr. Rahn has compared the work of breathing at different frequencies and depths to the extra oxygen required for the same performance as measured by Liljestrand. The results are shown in Fig. 2. The dotted lines represent work and the solid lines the oxygen. The ratio between the two scales is arbitrarily arranged to give the best fit. The ratio is 1 to 20 which indicates an efficiency of 5%. The parallelism between these two sets of curves is quite satisfactory and supports the validity of the method of calculating the work.

The relaxation pressure curve can also be used to calculate the work of pressure breathing if one knows in addition how far from its relaxation position the chest is at every pressure. This information is given from the graph of Fig. 1 where the position of the tidal air at every pressure is indicated by the double arrows. The upper end of each arrow represents inspiration and the lower end expiration. The total work of expiration is therefore represented by the rectangular area between

this arrow and the ordinate at zero pressure. That part of this area which lies between the curve P_{-} and the ordinate is work performed by the elastic potential energy of the thorax and lung and the remainder, between the arrow and the P_{-} curve is taken as the active work of expiration.

Under normal conditions at zero pulmonary pressure there is no expiratory work but only inspiratory work. The expiratory phase is completely passive and the point of relaxation is at the end of expiration. As the pressure becomes more positive the work of inspiration becomes less and at 7 mm Hg all the work is expiratory. At this point the end of inspiration is on the relaxation pressure curve. Inspiration is therefore completely passive and expiration is the active phase. It is noteworthy that at an intermediate pressure of 3.5 mm there is both inspiratory and expiratory work but the sum of the two is less than the inspiratory work at normal pressure. A small amount of PP therefore actually decreases the work of breathing. As the pressure increases still further inspiration is stopped before the muscles are completely relaxed and the expiratory muscles are always active. During inspiration the air pressure passively inflates the chest to some degree and stores some potential energy in the chest wall. This potential energy is available to assist in expiration but it is not sufficient to expel the air without the added force obtained from expiration. At a pulmonary pressure of 30 mm Hg the net work which the muscles must do is 10 times as great as normal. When breathing against negative pressures the work increase similarly but in this case it is the work of the inspiratory muscles which is concerned. This is the situation which obtains when one wades about in water up to his neck because the inspiratory muscles must continually resist the pressure of the water.

It is a point of considerable interest that in continuous pressure breathing the chest never completely relaxes. Instead the expiratory muscles continuously resist inflation even though this means more work. If they would completely relax at the end of each inspiration and permit the chest to inflate to its equilibrium position the work of breathing would be no greater under pressure than it is normally. It seems possible that this reflex or instinctive resistance to inflation represents what might be called an "effort" to avoid the evils of overinflation. The greater the volume of the lungs the greater the difference in pressure between the inside and the outside of the lung wall and hence the greater the danger of pneumothorax or emphysema. The fatalities due to inflation of the lungs in submarine escape operations are well known. If the lungs can be kept at the normal volume either voluntarily or by counter pressure they can stand very large pressures without danger because the absolute amount of pressure absorbed by the lungs is constant and an increment in pressure in the lungs results in an equal increment in pressure in the intrathoracic space and veins. Thus the "wisdom of the body" balances the dangers of overinflation against the dangers of overwork and strikes a happy medium.

The purpose of pressure breathing is of course to supercharge the aviator at a given altitude in order to secure better operation because of the higher tension of oxygen. It is to be expected therefore that with a given amount of pressure in the mask the subject will react much as he would if the whole body were exposed to the pressure. Provided the differential pressure is not sufficient to cause serious

circulatory disturbances on respiratory fatigue this seems to be the case. The actual average gain in altitude as indicated by performance tests seems to be equal to this theoretical amount.

The actual gain in oxygen tension however is not always equal to the gain in total pressure. This depends upon the rate of breathing. If the ventilation is so maintained that the alveolar pCO_2 remains constant then all the added mask pressure appears as added oxygen tension. If PB results in a decrease in the ventilation the added mask pressure is divided between pO_2 and pCO_2 in accordance with the ventilation equation. At air breathing altitudes the gain in oxygen tension is only 1/8 of the added mask pressure when the pCO_2 remains constant. This circumstance makes it difficult to gain much altitude tolerance by voluntarily developing pressure in the lungs against a closed glottis at an altitude of say 25,000 feet as recommended by Commoner. The effort of doing this increases the oxygen requirement by a considerable degree and further nullifies the advantage derived from the procedure. The gain in oxygen saturation which results from this procedure can be shown to be due almost entirely to the over-ventilation which accompanies the maneuver. (C.A.M. No. 304).

Experiment has shown that on the average the alveolar pCO_2 remains unchanged during continuous pressure breathing. During intermittent PB however there is usually some hyperventilation and the alveolar pCO_2 falls. If the alveolar ventilation is approximately doubled the alveolar pCO_2 will fall below 20 mm and signs of acapnia may be expected if the condition is long continued. This is not surprising because intermittent PB usually involves a higher pressure during inspiration than during expiration. This may be thought of as setting up reflexes or afferent impulses of such a nature that they "deceive" the respiratory center into "overestimating" the amount of ventilation which is being accomplished. If the acapnia continues there is some diminution in the ventilation but it seldom comes back to normal.

Another reason for the overventilation at the higher altitudes is that the increased pressure compresses the gas in the lungs and so intermittently drives more oxygen into the same volume. At a sufficient altitude the ratio of mask pressure to ambient pressure may be made equal to the ratio of tidal volume to total lung volume and when that is the case the lungs would obtain adequate ventilation even though the subject stopped breathing altogether and left his chest in a fixed position but exposed to the regular alternations of pressure. It is no wonder that the respiratory center is not properly equipped to deal with an experimental condition of this sort.

Intermittent as opposed to continuous pressure breathing recommends itself to the aviator because it avoids the extra work and fatigue of breathing against continuous pressure. This has the disadvantage however that the mean pressure is much lower than in continuous pressure breathing unless the peak pressure is made excessively and indeed intolerably high. When the pressure during expiration falls to zero, intermittent PB at a reasonable peak pressure (perhaps 35 cm H_2O) is less advantageous than continuous pressure breathing at the highest pressure that can be tolerated with reasonable comfort (15 to 20 cm H_2O). If, however,

the expiratory pressure is not allowed to fall to zero but is merely lowered enough to make expiration easy, although not necessarily passive, then the mean pressure may still be kept high enough so that intermittent PB will be able to compete successfully with continuous PB as a means of gaining altitude. This type of breathing can be accomplished with the Bennett valve but direct comparisons between this valve and continuous PB in the same subjects have not been made in a sufficient number of cases to justify a statement concerning the relative merits of this method.

If a little hyperventilation were an advantage at high altitudes then intermittent PB would be the method of choice. It certainly gives better arterial saturations than continuous PB but the performance depends upon the amount of hyperventilation which is allowed to occur. A high degree of acapnia is obviously disadvantageous but at every altitude there is nevertheless an optimum pCO_2 and the ventilation should be great enough to reach this value for best results. In their effects on the cerebral circulation acapnia and anoxia are antagonistic, the former causing constriction and the latter dilation of the vessels. This suggests that it might be possible to balance acapnia against anoxia at the highest altitudes and still remain in good condition. Experiments show however that in their effects upon performance the effects of acapnia and anoxia are additive. To show this we have made performance tests at different oxygen tensions or altitudes and at different CO_2 levels, varied by the use of the pneumolator and by increasing dead space.

It is found, therefore, that there is an optimum pCO_2 at each altitude and there is also a range of pCO_2 tensions at each altitude at which hyperventilation is beneficial. In general anoxia and acapnia are additive rather than antagonistic in their effects. This conclusion is supported by evidence from Blankenhorn and Ferris (12) who find that a given degree of acapnia is more harmful at high altitudes than at ground level as judged by the mental awareness of the subject and the frequency of the "brain waves".

This study represents a beginning in the solution of this problem but more work is required before a completely satisfactory answer is obtained. Valuable data have been obtained from many other investigators. Nims and his colleagues (10 and 11) have reported cases in which higher CO_2 levels appear to improve the performance. On the other hand, Hodes and Larrabee (9) have reported a series of flights in which the poorest performances were recorded for those who ventilated the least. A more comprehensive picture is obviously needed. Thereafter we need data to indicate what fraction of normal military personnel can be counted upon to ventilate to the optimum degree when guided by their own reflexes and how many set their alveolar CO_2 either too high or too low. Information of this sort will make possible an intelligent choice between the respective merits of continuous and intermittent pressure breathing devices. The only alternative is a direct experimental comparison with an adequate number of subjects.

One other feature of hyperventilation deserves mention because it is often advanced as an argument against hyperventilation which is generally depicted with some exaggeration as one of the most pernicious of high altitude hazards.

I refer to the Bohr effect. Although lowered pCO_2 favors the uptake of oxygen in the lungs it may be argued that it prevents the unloading of oxygen in the tissues and so does more harm than good. A detailed analysis of this situation cannot be given here, but it indicates that a decrease in the alveolar pCO_2 does not become a disadvantage until the percentage saturation of the blood reaches a level of about 95%. Under ordinary conditions at altitude therefore an increase in ventilation will increase the saturation of the arterial blood and will permit the same carriage of oxygen with either a fall in cardiac output or a rise in venous pO_2. When the arterial saturation reaches 95% however, then any further lowering of the alveolar pCO_2 and increase of pO_2 will result in a lowering of the venous pO_2 unless accompanied by a further increase in cardiac output. Either of these results must be regarded as disadvantageous since the venous pO_2 represents the diffusion gradient from blood to tissues and is properly regarded as the final objective of all circulatory and respiratory adjustments. An increase in cardiac output is disadvantageous because of the increased oxygen required for the purpose by the heart muscle. We conclude therefore that hyperventilation is disadvantageous only because of the deterioration in performance which the acapnia produces and not because of interference with the transport of oxygen by the Bohr effect.

The essential acute compensations for altitude are (1) an increase in the ventilation and a lowering of the carbon dioxide tension level in the lungs, i.e. a more equitable sharing of the total pressure between oxygen and carbon dioxide in the lungs and (2) an increase in the cardiac output in order to keep the mean oxygen tension in the venous blood and hence in the brain tissue as high as possible.

A few other miscellaneous findings concerning pressure breathing may be mentioned. It has no effect upon the incidence of bends, favorable or otherwise. [Gray (13) Gressley, Ferris, Conn]. The discomfort of breathing is diminished at higher altitudes where the less dense air permits easier movement at points of turbulence. Counterpressure by a pneumatic vest and pants improves the respiratory tolerance for pressure and has enabled Henry and others to reach an altitude of 58,000 ft. for a brief period before the hands started to swell (6)*. Counterpressure does not however diminish the loss of fluid from the blood (7) which otherwise occurs (3) since the venous pressure is higher than without counterpressure. There is no histological evidence of damage to internal organs after pressure breathing in dogs (8). According to Gagge pressure breathing raises the useful ceiling 1,000 feet for every 3 mm of Hg. This is a useful index for altitudes around 46,000 feet although 4 mm Hg might be taken as a more conservative estimate. In case of fainting, breathing continues in the unconscious subject in spite of the pressure and the subject recovers spontaneously at lower altitudes. (S. C. Allen, Wright Field, Gressley, Conn). The added tightness of the mask which is required for PB is a source of some extra discomfort which may discount to some extent the advantages derived from the extra oxygen.

SUMMARY

The application of pressure breathing brings into play two main disadvantages

*Further technical improvements since the time of this report have enabled the same workers to react much higher altitudes.

(1) the increased work and fatigue of breathing and (2) a possible decrease in the cardiac output. Both of these factors limit to varying degrees in different individuals the amount of pressure that can be tolerated. The first of these advantages can be mitigated by the use of intermittent rather than continuous pressure but this brings out a third hazard, i.e. hyperventilation and acapnia. In order to assay the relative advantages of continuous and different types of intermittent pressure breathing it is therefore necessary to know what the optimum carbon dioxide level is at every altitude in different people and further to what degree different people will instinctively attain this optimum level if left to themselves. Both of these questions need further study and both are fundamental to the whole problem of high altitudes as well as the more specific problem of pressure breathing.

With moderate amounts of pressure (10-15 mm Hg), PB effectively simulated the higher pressure and higher oxygen tension of a lower altitude and improves the performance accordingly.

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PRESSURE BREATHING

by

Wallace O. Fenn

Summary of talk given at Army Chemical Center at a Conference on Treatment of Gas Casualties, June 27-28, 1949

Pressure breathing is used to gain altitude tolerance by increasing the over-all pressure in the lungs and, therefore, the partial pressure of the oxygen. The gain in altitude tolerance will depend chiefly upon this increase in the partial pressure of the oxygen. A chart was presented which showed exactly what gain in altitude tolerance in feet would be expected at any particular altitude and any mask pressure. The greater the mask pressure, the greater the gain in altitude tolerance and the greater the altitude or the lower the total pressure, the greater the gain in altitude tolerance measured in feet for the same increment of pressure. Many arterial punctures at altitude with pressure breathing by Barach et al, Dill et al., Taylor and Marbarger have shown that the same increment in oxygen saturation of the blood is caused by an increment of 10 mm. in the mask or by an increment of 10 mm. in the total barometric pressure.

This statement requires, however, some qualification for it depends upon the effect of the pressure breathing on the ventilation of the lungs. At altitude one is faced with the problem of dividing the total available pressure between oxygen and carbon dioxide in the most advantageous manner. Rapid breathing raises the oxygen pressure in the lungs but lowers the carbon dioxide pressure so much that signs of acapnia may appear. The same dilemma occurs in pressure breathing (PB). If the breathing under PB is so regulated that the alveolar carbon dioxide pressure remains the same as before PB, then all of the excess pressure appears as increased oxygen pressure. This is the case at least when the inspired gas is pure oxygen. If the inspired gas is air then only about one fifth of the excess pulmonary pressure appears as oxygen partial pressure in the alveoli. Conversely the breathing might be so regulated that all of the excess pressure appears as increased partial pressure of carbon dioxide in the alveoli while the oxygen pressure remains the same. Experience shows that most subjects actually utilize the excess pressure as oxygen with little or no change in alveolar carbon dioxide pressure.

Continuous pressure breathing (CPB) is probably more advantageous than intermittent pressure breathing (IPB) largely because it is difficult to obtain so great a mean excess pressure if it is only applied intermittently; the peak pressure in IPB would have to be uncomfortably high if the mean pressures were made equal to that in CPB. Intermittent pressure breathing with the positive pressure phase in inspiration gives a high oxygen saturation of the blood because it generally leads to some degree of hyperventilation but the alveolar carbon dioxide is simultaneously made rather too low for best performance. In some individuals a combination of the two methods with some positive pressure all the time but more in inspiration than in expiration would be better than constant pressure because it leads to an increase in ventilation (such an arrangement is obtained with the Bennett valve and requires less

effort). Other individuals tend to hyperventilate even with continuous pressure breathing and in their case the reverse would be true.

Pressure breathing then does not eliminate the breathing dilemma; you still have to decide what you are going to do with your extra pressure, whether you are going to use it for carbon dioxide or for oxygen. I believe it is still a question whether a man left entirely to himself at altitude will be able instinctively or reflexly to select an optimum division between carbon dioxide and oxygen.

Pressure breathing brings with it a number of other difficulties which are common to a man in high altitude as well as to a patient. One of these is the discomfort of the mask which must be held tightly against the face to avoid leaks under pressure. The smaller the mask, the less total pressure required and the less discomfort. There is also the danger of pneumothorax or emphysema; you might break a hole in the lung or force a little air into the mediastinum and thence down to the abdomen or up into the neck; you may get some pain then from breathing if the pressure is too high. The tendancy of the lungs to rupture has been measured and it is found by Henry that an excised lung would stand pressures up to 30-60 m.m. Hg. but for the lung in the chest it took 60-100 mm. Hg. to cause a rupture. It was concluded that 50 mm. was a safe pressure for a man to breathe. Of course, if you protect the chest and prevent its expanding by a vest of some kind, then the danger is less. It is only when you let the chest expand that you increase the danger of making a hole in the lung. It is the difference in pressure between the inside and the outside of the lungs that causes the break. If the volume of the lung is kept normal either by continual muscular effort or by a counter pressure vest then the lung volume is normal and the danger of breakage is no greater than normal. Some exceptions to this might occur in the lungs under pressure at "soft" points in the chest, over the large veins, etc.

A third major difficulty encountered in pressure breathing is the increased respiratory effort which is required. Discussions of this point involve a knowledge of the simple mechanics of pressure breathing. This is best illustrated by a pressure volume diagram of the lung. Such a diagram shows the maximum inspiratory or expiratory pressures which can be exerted by the respiratory muscles at all lung volumes from maximum expiration to maximum inspiration. Volumes may be plotted vertically and positive and negative pressures to the right and left respectively. The area of such a pressure-volume chart represents the theoretical maximum work of which the respiratory muscles are capable. Such a diagram represents the chest and lungs in activity.

The passive position of the chest at all positive or negative pressures can also be plotted on the same diagram and gives a single line known as the "relaxation pressure curve." Such a curve gives a measure of the elastic forces which the muscles must overcome in order to inflate and deflate the chest from its resting position. Again the area on the chart under a relaxation pressure curve will represent the elastic work of breathing. During pressure breathing, however, it can be shown that the chest does not follow this passive relaxation pressure curve. Instead the passive inflation of the chest expected from the positive intrapulmonary pressure is actively resisted throughout the cycle by the expiratory muscles. This causes a substantial increase in the calculated work of breathing. The greater the pressure

(either positive or negative) the greater the work. This increased work should result similarly in an increase in the required rate of oxygen consumption. Actually Chassis at New York University made measurements of the oxygen needed for pressure breathing and reported no measurable increase. One must suppose, however, that the increase was too small to detect by the methods employed. One of the errors which it is difficult to allow for in such a measurement of the oxygen consumption is the considerable increase in the lung capacity when pressure breathing begins. This causes an expansion of the lungs and traps a certain amount of gas which has to be distinguished from oxygen actually used. Whether or not this increased oxygen is obvious experimentally it is certainly true that pressure breathing is subjectively harder than normal breathing. The difficulty diminishes at altitude due to the diminished resistance to motion of the air. During pressure breathing the subject is never at complete rest during the breathing cycle but he is always "fighting back" against the inflation. During pressure breathing the inspiratory reserve (complemental air) diminishes and the expiratory reserve (supplemental air) increases.

The work of breathing can be broken down further into the elastic work and the viscous work. The latter represents resistance to air flow and resistance to deformation of the tissues. Work of moving the gases or tissues in expiration is usually passive and is performed at the expense of elastic potential energy stored in the system during inspiration. In pressure breathing the reverse is true and expiration becomes the active phase. There is no opportunity for the expiratory muscles to relax except briefly during the process of passive inspiration.

The work of moving the air in breathing is being measured in my laboratory by the method of intermittent obstruction of flow. The flow is momentarily interrupted at any phase of the cycle by a shutter in the breathing tube and the rise or fall of pressure on the mouth side of the obstruction is taken as a measure of the mouth to alveoli pressure gradient at that moment. If the velocity of air flow is measured simultaneously then the gradient required for a given rate of flow may be taken as a measure of the resistance of the breathing tubes to air flow. Dr. Otis has made measurements of this resistance at different altitudes and with different mixtures of helium and nitrogen and has found that the resistance (R) follows the equation of Rohrer $R = kV + k'V^2$ where V is the velocity of flow and k and k' are constants. The first term represents the resistance to laminar or stream line flow and the second term, varying as the second power of the velocity, represents the resistance due to turbulence. His findings showed that k is independent of the altitude but k' varies directly with the density of the gas, in accordance with theoretical predictions.

Of special importance for pressure breathing is the most recent finding of Dr. Otis that no measurable change in resistance occurs with pressure breathing. This is perhaps somewhat surprising in view of the findings of Dr. Barach and also Dr. Gerard, from X-ray measurements, that pressure causes a measurable enlargement of the diameters of the bronchioles. The experimental method used by Otis does not, of course, admit of great accuracy and some decrease of resistance may have escaped detection. It may also be, however, that so much of the resistance is at the angles and bifurcations of the tubes and so little in the laminar flow in the tubes themselves that mere enlargement of the tubes would have little real influence on the result. Anyhow, from these preliminary observations, it does not seem reasonable to recommend pressure breathing for gas casualties on the grounds that it enlarges

he tubes and thus decreases the resistance to the breathing although this is an argument which is sometimes advanced.

The most important hazard of pressure breathing is the circulatory embarrassment. This depends chiefly upon the increase in the intrathoracic pressure which rises with pressure breathing. The magnitude of this rise depends upon the inflation of the lungs. The more they inflate the more of the applied pulmonary pressure they absorb and the less is the fraction passed on to the intrathoracic space. If the lungs expand with pressure along the relaxation pressure curve all of the pulmonary pressure is absorbed by the lungs and chest. Until the chest expands to about 70% of maximum inspiration, all of the pressure is absorbed by the lungs. Below this point the chest would naturally expand if the lungs did not cause it to collapse (negative intrathoracic pressure). In normal pressure breathing, however, the lungs do not expand along the relaxation pressure curve as already mentioned and only about half of the applied pressure is absorbed by the lungs. Thus if the mask pressure is increased 10 mm., the intrathoracic pressure will increase about 5 mm. and in turn the venous pressure will increase 5 mm. so that a pressure gradient of normal magnitude is maintained in the veins between the periphery and the heart. So long as this continues, the venous return and the cardiac output remain normal. At the pressures usually used in PB, however, a decrease of perhaps 15% in the cardiac output may be expected.

Along with the increase in the venous pressure there is a corresponding increase in the arterial pressures because the base line of the circulation, the intrathoracic pressure, has gone up. This finding has one interesting theoretical consequence because it shows that the level of the arterial pressure is not regulated exclusively by the pressure receptors in the cardiac sinus. These receptors are not exposed to the increased intrathoracic pressure so they would be expected to maintain the arterial pressure at the same level relative to the atmospheric pressure. Instead, the arterial pressure appears to be regulated at the same level relative to the intrathoracic pressure, possibly by receptors in the aorta.

There is evidence that pressure breathing causes peripheral vasoconstriction. This appears clearly when the volume of the leg is recorded continuously in a plethysmograph. If pressure breathing is initiated, this volume of the leg increases passively because of the rise in the venous pressure. If, however, a pneumatic cuff is placed around the leg above the plethysmograph and inflated to a level above the venous but below the arterial pressure then the volume of the leg increases by passive inflation from the arterial side but it is protected from passive responses to changes in venous pressure by the cuff. If under these conditions pressure breathing is begun, the volume of the leg diminishes due to peripheral vasoconstriction.

Other evidence of this same vasoconstrictor reaction is seen in the diminution of the volume pulse in the finger when pressure breathing begins and the decrease in volume of flow through the finger as shown by the plethysmographic method (Fenn and Chadwick). In addition there is also a prompt decrease in the skin temperature of the fingers. Just where this vasoconstrictor reflex originates it is difficult to say. A similar vasoconstriction occurs without pressure breathing as a result of a single deep inspiration or a single deep expiration as shown by DeLalla in our laboratory. It occurs with pressure breathing even when the expansion of the lung and chest is

prevented by counter pressure of a vest. The reflex, therefore, does not come from stretch receptors in the lung itself. Just what purpose is served by such a reflex it is also difficult to say. It presumably increases the arterial pressure but since this is elevated anyway due to the increase in the intrathoracic pressure, further provision for the maintenance of adequate cerebral flow would seem unnecessary.

Another important consequence of pressure breathing is the loss of water to the tissues which results from the increase in the venous and capillary pressure. Henry has reported that pressure breathing for a half hour at a pressure of 30 mm. Hg. causes a loss into the tissues of 4% of the blood volume. A similar result was obtained by Hyman and Goodman.

Pressure breathing does, therefore, suffice to cause movements of water between capillaries and tissues and it has been proposed that it could serve equally well in the lungs to cause flow in the reverse direction, from the alveoli back into the blood, thus relieving the stress of pulmonary edema. On theoretical grounds it seems clear that the onset of pressure breathing would increase the resistance of the pulmonary circulation by tending to cause collapse of the pulmonary capillaries which are exposed to the intrapulmonary rather than the intrathoracic pressure. It was argued at the conference, however, that any decrease in flow in the capillary would result in a rise in pressure in the capillary until the normal gradient was reestablished. It is difficult to believe, however, that this compensation is complete. The pressure around the heart (intrathoracic) has increased approximately half as much as the pressure around the pulmonary capillaries and the flow is somewhat less than before. Heinbeckers for example has shown that inflation of the lungs from the trache diminishes the blood flow whereas inflation by diminution of the pressure around the outside of the lungs increases the blood flow. Thus some tendency to cause reabsorption of fluid might be expected from pressure breathing. However, the pressure recommended for use on patients with pulmonary edema is only 4-5 mm. Hg. and the capillary pressure normally about 8-9 mm. Hg. Thus the outward differing pressure could not be decreased by more than 2 mm. at the most since the capillary pressure would go up 2-5 mm. at least with P.E. Considering that the colloid osmotic pressure which tends to absorb water is of the order of 25 mm. Hg. and since some of this would presumably remain even after an increase in permeability due to some irritant material, it does not seem likely that the pressure breathing could become a very potent factor in the capillary balance. This conclusion is in accord with the many experiments on animals with pulmonary edema from irritant gases in which no beneficial effect from pressure breathing was ever established. Nevertheless, in view of the clinical reports of the efficacy of pressure breathing in pulmonary edema, the writer at least would prefer not to be deprived of the alleged benefits of this procedure in case he were ever in a condition to require treatment.

The question is still raised from time to time whether pressure breathing by negative pressure applied to a mask is the same as pressure breathing by negative pressure applied to the outside of the body, except the head. I think it can be said that if the negative pressure were applied to everything except the mask, then the two would be identical. The pressure on the neck does not appear to be very important in the process. The only exception to this statement might be during the first fraction of a second after the pressure is applied to the mask during which time the pressure wave is being transmitted to the alveoli. The negative pressure

applied to the outside of the body is transmitted practically instantaneously to the lungs through the incompressible fluids of the body. Efforts to combine these two methods of artificial respiration or pressure breathing to obtain a more effective combination seem to us, therefore, theoretically futile.

Mechanics of Breathing in Man[1]

ARTHUR B. OTIS, WALLACE O. FENN AND HERMANN RAHN.

THE MECHANICAL WORK done by the respiratory muscles in producing the movements of breathing has been studied relatively little by physiologists. Although most text-books of physiology give values for the work done by the heart, similar estimates for the work of breathing are lacking. The classic contributions of Rohrer (1–3) lay the foundation for this subject, but only a few pertinent papers, notably those of Neergaard and Wirz (4), Vuilleumier (5), Bayliss and Robertson (6), and Dean and Visscher (7), have since appeared.

The material presented below, although based on data which are neither sufficiently precise nor extensive enough to furnish an exact description of the mechanics of breathing, constitutes an approximate analysis, which we have found valuable as a way of thinking about certain respiratory problems.

FORCES INVOLVED IN BREATHING

From the work of previous investigators and on the basis of *a priori* reasoning, we should expect that the respiratory muscles in carrying out the breathing movements would have to overcome several types of resisting forces. These forces will be mentioned briefly now and considered later in more detail. The chest and lungs are elastic in nature and must be stretched during inspiration to accommodate an increased volume. The air in moving through the respiratory tract encounters viscous and turbulent resistance, and there is probably some additional non-elastic resistance associated with deformation of tissues, and with the sliding of organs over one another when they are displaced. Finally, since the system is almost continuously accelerating or decelerating, inertia should be mentioned as a possible factor. The calculations of Rohrer (3), however, indicate that the force required for acceleration must be ordinarily very small, and we shall, in general, consider it negligible. Another factor of relatively inconsequential magnitude is the kinetic energy imparted to the air.

[1] This work was completed under contract between the University of Rochester and the Air Materiel Command, Wright-Patterson Air Force Base, Dayton, Ohio. Some of our earlier work was reported in C.M.R. Report No. 430, May 10, 1945 and in *Federation Proc.* 6: 173, 1947. An abstract of a preliminary report, presented before the National Academy of Sciences, appears in *Science* 110: 443, 1949.

Elastic Forces. If a person relaxes his respiratory muscles completely, the lungs assume a volume close to that which is customary at the end of a normal expiration, the mid-capacity or *relaxation volume.* At this volume the elastic forces of the chest must be equal and opposite to those of the lung. When the chest-lung system is displaced to any other volume, elastic forces which oppose the displacing force are developed. The method of measuring these elastic forces as *relaxation pressures* and a curve showing the relationship between relaxation pressure and lung volume have been presented in a previous paper from this laboratory (8). The reciprocal slope, $\Delta P/\Delta V$, of the relaxation pressure curve is the elastic resistance or 'elastance' (pressure required to produce unit change in volume (6, 7)). Although the relaxation pressure curve is not linear, it is approximately so over a considerable part of its range, and as a first approximation the elastance may be expressed by the following equation:

$$P_{el.} = KV \qquad (1)$$

where K is the elastance and $P_{el.}$ is the pressure developed when the displacement from the relaxation volume is V.

Air Viscance and Turbulence. A method for estimating the magnitude of the viscous and turbulent forces that must be overcome in moving air through the respiratory tract has been described previously (9, 10), and data have been presented which indicate that the relationship between these forces and the velocity of air flow may be described approximately by the following equation:

$$P_{alv.} = k_1\left(\frac{dV}{dt}\right) + k_2\left(\frac{dV}{dt}\right)^2 \qquad (2)$$

where $P_{alv.}$ is the pressure gradient between alveoli and mouth that is required to move the air with a velocity (dV/dt). The constants k_1 and k_2 are the air *viscance*[2] and the *turbulent resistance*, respectively.

An example of the sort of record from which data were obtained for purposes of the present investigation is shown in figure 1, and the points obtained from measurement of records made on *subject R* are shown in figure 3. The parabola was fitted to these points by the method of residuals.

Resistance Associated with Tissue Deformation. It does not seem feasible to measure directly the non-elastic resistance associated with tissue deformation, but an estimate may be obtained in the following fashion. A trained subject is placed in a Drinker respirator and is instructed to relax as completely as

[2] Our usage of the word 'viscance' in this paper is implicit in *equation 2* and may be used synonomously with 'viscous resistance'; it is expressed in dimensions of pressure per unit flow of respired gas. 'Viscance' was defined by Bayliss and Robertson (6) as "the viscous force per unit deformation" or "viscous pressure per unit of tidal air volume." Dean and Visscher (7), however, use the same term to mean "viscous resistance to a unit velocity of flow." Although the definition of Bayliss and Robertson was stated to make 'viscance' analagous to 'electrical resistance,' we believe that our usage of the term is a better analogy.

possible so that his breathing movements are produced by the alternating pressure within the respirator instead of by the action of his respiratory muscles. The pressure gradient between the respirator and the mouth of the subject and the velocity of air flow are simultaneously recorded. The pressure recorded at any moment is, of course, that required to overcome the total resistance, and since the elastance and air viscance and turbulent resistance can be obtained as described above, the non-elastic tissue resistance can be estimated by difference. Figure 2 shows a sample record obtained in this type of experiment.

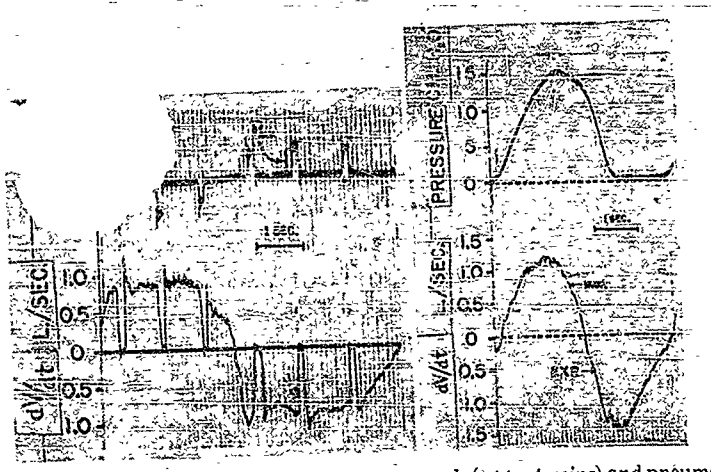

Fig. 1 (*left*). SIMULTANEOUS RECORDS of pressure at mouth (*upper tracing*) and pneumotachogram (*lower tracing*). In pneumotachogram, inspiration is above and expiration below baseline. Sudden changes in pressure at mouth and simultaneous interruptions of air flow were produced by brief closure of solenoid valve located in airway between mouth and pneumotachograph. Method of estimating alveolar pressure ($\bar{P}_{alv.}$) is indicated.

Fig. 2 (*right*). SIMULTANEOUS RECORDS of pressure gradient between mouth and inside of Drinker respirator (*upper tracing*) and pneumotachogram (*lower tracing*). *Subject R.*

A useful way of representing some of the data that can be obtained from such a record is shown in figure 4 in which pressure is plotted against accumulated volume for one breathing cycle. The method of constructing such a diagram will now be described.

The velocity of flow and the simultaneous pressure were measured and tabulated for each 0.1-second interval of the record of the respiratory cycle shown in figure 3. Then starting at the beginning of inspiration each 0.1-second interval of the flow curve was integrated by multiplying the mean velocity of flow during each period by 0.. second. This gave the volume that flowed during each 0.1-second period. These volumes were then added in a cumulative fashion and the total volume at the end of each time interval was plotted against the corresponding pressure gradient that existed at the end of

that interval. The plotted points determine the solid lines that form the large loop in figure 4.

This closed curve represents the relationship between the changes in the volume of the lung during the respiratory cycle and the external forces (as represented by the pressure gradient between the respirator and mouth) acting to produce this change. At two moments (when the cycle reverses from in-

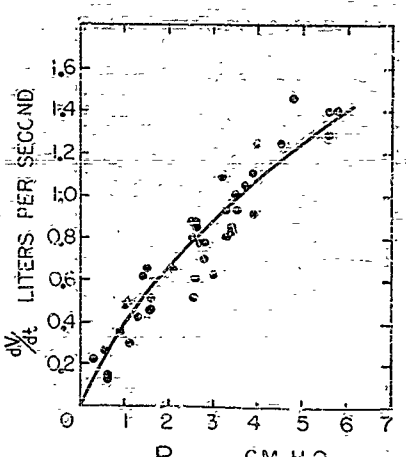

Fig. 3. RELATIONSHIP between instantaneous rate of flow of respired gas and pressure gradient between alveoli and mouth for *subject R.* Curve drawn through points represents equation:

$$P_{alv.} = 1.7\left(\frac{dV}{dt}\right) + 1.9\left(\frac{dV}{dt}\right)^2.$$

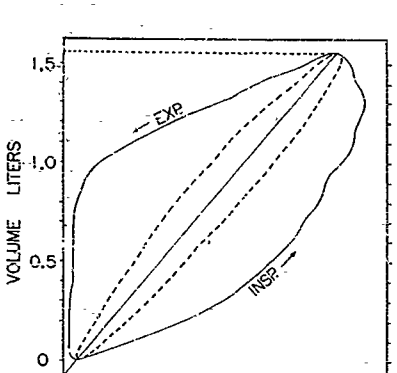

Fig. 4. RELATIONSHIP between volume of respired gas and pressure gradient during one respiratory cycle for *Subject R.* For explanation, see text.

spiration to expiration and vice versa) no air is being moved in either direction. At these instants, therefore, the total force acting is being used to maintain elastic tension that has been developed, inertia being assumed to be negligible. If we assume a linear relationship between elastic pressure and lung volume, then the diagonal in figure 4 represents this relationship. Approximately, it is a segment of the relaxation pressure curve.

Some of the information represented by figure 4 may be summarized as follows. As the lung volume is increased during inspiration, the total pressure

gradient between the mouth and the inside of the respirator is represented by the abscissal distance from the axis of ordinates to the inspiratory loop. Of this total inspiratory pressure ($P_{in.}$) at any given lung volume, a certain amount ($P_{el.}$), represented by the abscissal distance from the axis of ordinates to the diagonal, is required to overcome elastance; the remainder ($P_{in.} - P_{el.}$) is the pressure required to overcome air and tissue viscance and turbulent resistance.

Expiration is produced by the elastic forces that were developed in the chest and lung during inspiration. However, the total elastic force is not available, in this case, for overcoming the viscous and turbulent resistances of expiration, because the pressure within the respirator continues to be negative especially during the first part of expiration. The pressure actually used in overcoming viscance and turbulence at any moment during expiration is of course ($P_{el.} - P_{ex.}$) where $P_{ex.}$ is the abscissal distance from the axis of ordinates to the expiratory loop, i.e. the pressure gradient between the mouth and the inside of the respirator during expiration. Under the conditions of the particular experiment illustrated in figure 4, the lung volume does not quite get back to the relaxation volume by the end of expiration; the respirator starts an inspiratory movement before expiration is as complete as it would be if more time were allowed.

The relationship between numerous values of ($P_{in.} - P_{el.}$) or ($P_{el.} - P_{ex.}$) and the corresponding velocities of flow is represented by the points plotted in figure 5. These data were obtained from figures 2 and 4 and other similarly plotted cycles measured on *subject R*. The parabolic curve drawn through the point S was fitted by the method of residuals and may be generally represented by

$$P_n = K'\left(\frac{dV}{dt}\right) + K''\left(\frac{dV}{dt}\right)^2 \qquad (3)$$

the slope of which represents the total viscous and turbulent resistance of breathing.

By subtracting the curve of figure 3 from that of figure 5 a relationship of the following form is obtained

$$P_t = k_3\left(\frac{dV}{dt}\right) + k_4\left(\frac{dV}{dt}\right)^2 \qquad (4)$$

Its slope represents the resistance associated with the non-elastic component of tissue deformation.

By means of *equation 4*, P_t was calculated for each 0.1-second interval of figure 2 and the resulting values were added to the corresponding values of $P_{el.}$ during inspiration and subtracted during expiration. These sums or differences were plotted against the cumulative volume for the corresponding time interval to form the loop indicated by the broken line in figure 4. The

abscissal distance from the diagonal to this loop is the pressure required to overcome non-elastic resistance of tissue.

Constants for *equations 1, 2, 3* and *4* evaluated as outlined above are recorded in table 1 for *subject R* and for two other subjects who were similarly studied. The values shown for each subject are based on measurements of several cycles.

Total Force Required for Breathing. The total force required for breathing is the sum of *equations 1* and *3* or

$$P_\Sigma = KV + K'\left(\frac{dV}{dt}\right) + K''\left(\frac{dV}{dt}\right)^2 \qquad (5)$$

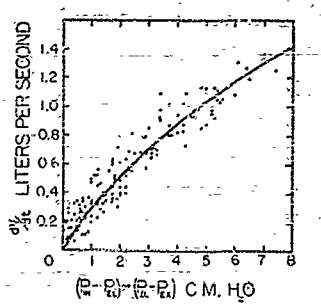

Fig. 5. Relationship between instantaneous rate of flow of respired gas and pressure required to overcome non-elastic resistance to breathing. *Subject R.* Curve drawn through points represents equation:

$$P_n = 2.7\left(\frac{dV}{dt}\right) + 2.1\left(\frac{dV}{dt}\right)^2.$$

Table 1. Values of resistance constants estimated for three subjects

Subject	Elastic resistance	Additional resistance of air		Additional resistance of tissue		Total additional resistance	
	K	k_1	k_2	k_3	k_4	K'	K''
	cm.H_2O/l.	cm.H_2O/(l/sec.)	cm.H_2O/(l/sec.)^2	cm.H_2O/(l/sec.)	cm.H_2O/(l/sec.)^2	cm.H_2O/(l/sec.)	cm.H_2O/(l/sec.)^2
R	8.00	1.7	1.9	1.0	0.2	2.7	2.1
B	9.38	3.2	0.8	1.0	0	4.2	0.8
D	8.19	2.9	1.4	0.6	0.1	3.5	1.5
Mean.....	8.52	2.6	1.4	.9	.1	3.5	1.5

THE WORK OF BREATHING

Another useful feature of the method shown in figure 4 of representing a breathing cycle is that area on such a diagram has the dimensions of work. For example, the area of the triangle formed by the diagonal, the horizontal broken line and the axis of ordinates in figure 4 represents the amount of work done during inspiration in overcoming elastic resistance. The area bounded by the diagonal and the curved line labeled *inspiration* is the additional work required to overcome the viscous and turbulent resistance of inspiration. This area may be subdivided into work done on non-elastic resistance of tissue (area between diagonal and broken line) and work done in overcoming air viscance and turbulent resistance.

The elastic energy stored during inspiration and represented by the triangle is available as a power supply for expiration. However, only that portion bounded by the diagonal and the curve labeled *expiration* is actually used in this instance to overcome viscous and turbulent forces; the remainder is expended in working against the continued action of the respirator which opposes expiration during the first part of this phase of the breathing cycle.

Table 2 summarizes measurements of the work of breathing and its fractions obtained by planimetric integration of diagrams such as that illustrated by figure 4. These data indicate that on the average 63 per cent of the total work done in inspiration was used in overcoming elastic forces, 29 per cent in

TABLE 2. WORK OF BREATHING IN DRINKER RESPIRATOR AT FREQUENCY OF 15 PER MINUTE

SUBJECT	TIDAL VOLUME	TOTAL WORK OF INSPIRATION	ELASTIC WORK OF INSPIRATION	WORK ON AIR DURING INSPIRATION	WORK ON TISSUES DURING INSPIRATION
	cm.³	*gm.-cm.*	*% of total*	*% of total*	*% of total*
R	1550	17,295	63.0	27.4	9.5
	1340	13,170	59.7	31.5	8.8
	950	6,265	61.5	27.8	10.7
	500	2,091	63.6	28.8	7.6
B	2275	47,660	66.8	25.8	7.4
	1620	23,665	69.2	22.7	8.1
	840	6,220	60.1	32.1	7.8
D	995	7,462	59.6	34.9	5.5
	1365	9,225	65.8	25.0	9.2
	1095	7,720	64.0	28.7	7.3
Mean Values.....			63.3	28.5	8.2

overcoming resistance associated with the movement of air, and 8 per cent in deforming tissues. These percentages apply, of course, only to the particular pattern of breathing employed in this experiment. As will be pointed out later, both the absolute and relative magnitudes of these factors depend to some extent on the particular pattern of breathing employed.

If one assumes that *equation 5* is reasonably valid, the information contained in it makes possible the estimation of the work of breathing for any breathing cycle for which the velocity pattern (pneumotachogram) is known. One method would be to calculate the corresponding pressures for numerous points along the velocity curve and then to follow the procedure described above that was used in getting the data of table 2. This empirical method is very tedious, however, and if one can describe the velocity curve by a simple mathematical expression, the work of breathing may be calculated in a more direct fashion.

For example, assume as a first approximation that the velocity pattern of inspiration is a sine wave (fig. 6). Then

$$\frac{dV}{dt} = a \sin bt \qquad (6)$$

where dV/dt is the velocity of air flow, a is the maximal velocity, and $b/2\pi = f$ is the frequency of breathing.

The tidal volume, V_T, is given by

$$V_T = \int_0^{\pi/b} a \sin bt \, dt = \frac{2a}{b} = \frac{a}{\pi f} \qquad (7)$$

The differential expression for work is $dW = P dV$ which by substitution from *equations 5* and *6* becomes

$$dW = KV \, dV + K' a^2 \sin^2 bt \, dt + K'' a^3 \sin^3 bt \, dt \qquad (8)$$

In this expression for the differential of work, the first term represents elastic work, the second viscous work, and the third work done in overcoming

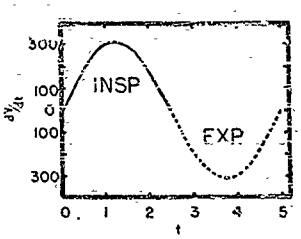

Fig. 6. IDEALIZED REPRESENTATION of pneumotachogram as sine wave. *Ordinates:* Flow of respired gas in cc/sec. *Abscissae:* Time in sec. In this example a mean ventilation of 6 l/min. with tidals of 500 cc. and frequency of 12 breaths/min. is assumed. Constants of *equation 6* in this case are, therefore: $a = 314$ cc/sec. and $b = 0.4\,\pi$ reciprocal seconds.

turbulent resistance. The total work done during a single inspiration of volume V_T and duration π/b may be obtained by integration of *equation 8* as indicated below

$$W = \int_0^{V_T} KV \, dV + \int_0^{\pi/b} (K' a^2 \sin^2 bt + K'' a^3 \sin^3 bt) \, dt \qquad (9)$$

$$W = \tfrac{1}{2} K V_T^2 + \tfrac{1}{4} K' \pi^2 f V_T^2 + \tfrac{2}{3} K'' \pi^2 f^2 V_T^3 \qquad (10)$$

The mean rate of doing work is the work per breath times the frequency of breathing.

Mean rate of work =

$$\tfrac{1}{2} K f V_T^2 + \tfrac{1}{4} K' \pi^2 (f V_T)^2 + \tfrac{2}{3} K'' \pi^2 (f V_T)^3 \qquad (11)$$

This is the inspiratory work per unit time but if it is assumed that expiration is passive, it is of course an expression of the total work of breathing per unit time as a function of tidal volume and frequency. If the tidal volume is divided into an effective or alveolar portion, V_A, and a dead space portion, V_D, *equation 11* becomes

Work per unit time =

$$\tfrac{1}{2}K\dot{V}f\left(\frac{\dot{V}_A}{f}+V_D\right)^2+\tfrac{1}{4}K'\pi^2(\dot{V}_A+fV_D)^2+\tfrac{2}{3}K''\pi^2(\dot{V}_A+fV_D)^3 \qquad (12)$$

where $V_A f = \dot{V}_A$ = alveolar ventilation.

By *equation 12* the rate of work of breathing can be calculated for any given alveolar ventilation, frequency and dead space. Figure 7 shows the calculated work per minute at various breathing frequencies when the alveolar ventilation is 6 liters per minute and the dead space is assumed to be constant at 200 cc., values which are reasonably typical for a resting subject.

In making these calculations the mean values for K, K' and K'' given in table 1 were converted to appropriate units so that $\dot{V}_A$ could be expressed in liters per minute and f in breaths per minute and rounded off for ease of computation. The equation as used was gm. cm. of work per minute =

$$5000f\left(\frac{\dot{V}_A}{f}+0.2\right)^2+150(\dot{V}_A+0.2f)^2+3(\dot{V}_A+0.2f)^3 \qquad (13)$$

Of special interest is the fact, illustrated by this graph, that for a constant alveolar ventilation there is a frequency which is optimal (in the sense of minimal work). This minimum occurs because when the frequency is too low, much elastic work is required to produce the large tidal volumes and when the frequency is too high, much work is uselessly done in ventilating the dead space with each breath.

The fact that the optimal frequency in this case is in the range ordinarily observed in the breathing of resting subjects suggests itself as an example of the principle of minimal effort according to which so many of the body functions seem to be regulated.

By differentiating *equation 12* with respect to f, setting the result equal to 0, and solving for $\dot{V}_A$ we have the general solution for the conditions of minimal rate of doing work.

$$\dot{V}_A=\frac{KDf+K'\pi^2Df^2+4K''\pi^2D^2f^3}{K-4K''\pi^2Df^2} \qquad (14)$$

Various values of f have been substituted in *equation 14* and the resulting curve is shown in figure 8 (curve labeled $W_{min.}$). This curve predicts that the greater the alveolar ventilation, the higher will be the frequency for the condition of minimal work. Since this curve actually applies to the condition of minimal inspiratory work, it can not be accepted for minimal total work unless expiration is completely passive. The curve labeled $W_V + W_T = W_E$ in figure 8 shows the frequency at which the work required for expiration (assuming this is the same as that required to overcome viscous and turbulent resistance of inspiration) becomes equal to the elastic energy stored during inspiration. Conditions represented by the area above this curve will, therefore, require the

active participation of the expiratory muscles. For alveolar ventilations greater than about 15 liters per minute, the curve $W_{min.}$, while defining conditions for minimal inspiratory work, will predict frequencies that are too high for minimal work of inspiration plus expiration. The curve $W_V + W_T = W_E$ defines, in a sense, conditions for minimal expiratory work in that it indicates conditions such that the elastic energy stored in inspiration is just enough to meet the needs of expiration. At the higher alveolar ventilations, however, the conditions demanded by this curve become absurd, because the required tidal volume becomes impossibly large. The conditions for a tidal volume of 4 liters are indicated for purposes of illustration, by the line $V_T = 4$.

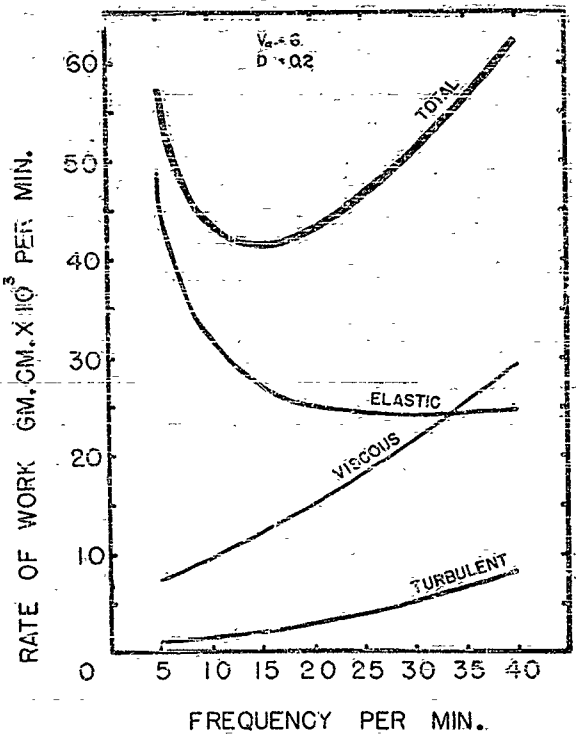

Fig. 7. RELATIONSHIP of elastic, viscous, turbulent, and total work of breathing/min. to frequency of breathing when alveolar ventilation is 6 l/min., and dead space is 200 cc. Curves calculated according to *equation 13*.

One might expect then that for the lower range of ventilations the optimal frequency would be defined by curve $W_{min.}$, but at the higher ventilations the optimal frequencies would lie between the curve $W_V + W_T = W_E$ and the dotted section of curve $W_{min.}$.

Several sets of data from the literature showing frequencies voluntarily chosen by subjects whose breathing was stimulated by added dead space, by CO_2 added to the inspired air, or by exercise bear out this expectation in a general way, as indicated by the plotted points in figure 8.

Although these considerations yield no exact description they do perhaps indicate roughly how various factors may interact to determine the frequency at which we breathe under various ventilatory requirements. It would be desirable, of course, to determine what the exact velocity patterns of inspiration and of expiration should be for optimal conditions. To do this would require a much more involved treatment which is probably not justified without more exact data as a basis.

The above discussion has been predicated on the principle of minimal effort but we do not wish to imply that this is the only principle involved. Another important consideration, especially in unusual situations, might be called the 'principle of maximal comfort.' If a patient with pleurisy, for example, finds that one pattern of breathing is less painful than another, it is likely that he will sacrifice a few calories for the sake of comfort.

Mechanical Efficiency of Breathing. Several investigators (11–13) have estimated the total energy required for breathing at various depths and frequencies by measuring the extra oxygen consumption during hyperpnea either voluntarily produced or stimulated by CO_2 added to the inspired air. The most comprehensive series of such measurements is that of Liljestrand (11), whose data are represented in part by the solid lines in figure 9.

On the same graph are plotted dotted lines representing the mechanical work (calculated by *equation 11*) required for the corresponding conditions of

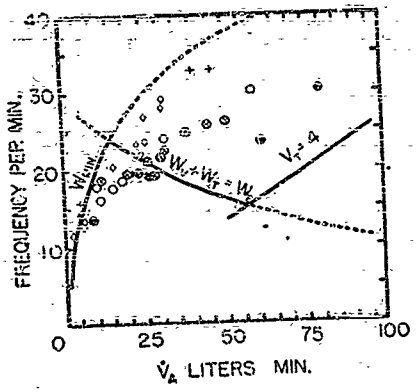

Fig. 8. FACTORS DETERMINING OPTIMAL BREATHING FREQUENCIES for various alveolar ventilations For explanation of curves, see text. Plotted points represent data from literature as follows: *open circles, subject K.M.*, Barcroft and Margaria (21); *solid circles, subject J.B.*, Barcroft and Margaria (21); *circles with X, subject J.J.*, Lindhard (22); *diamonds, subject J.B.*, Hansen (23); *crosses, subject G.L.*, Liljestrand (11). Alveolar ventilations calculated from recorded total ventilations by assuming dead space of 200 cc.

ventilation and frequency. The scale of ordinates for the calculated mechanical work has been adjusted so that it is equal to 5.4 per cent of that for the extra oxygen consumption. This figure is the average of 19 values obtained by dividing each of Liljestrand's measurements into the mechanical work calculated for the corresponding condition. The individual values for mechanical efficiency obtained in this fashion varied from 3.0 per cent for a frequency of 5 and a ventilation of 20 liters per minute to 7.6 per cent for a frequency of 20 and a ventilation of 30 liters per minute.

This variation in the calculated efficiency is reflected, of course, in the discrepancies between the curves for total energy and those for mechanical work in figure 9, because exact agreement between these two families of curves would require that the calculated efficiency be constant for all conditions.

Part of this apparent variability in efficiency under different conditions can, of course, be attributed to the inexactness of our equation for calculating

mechanical work, but part is probably real, since it is well known that the efficiency of muscular work varies with muscle length and load.

In Liljestrand's experiments the breathing was voluntarily regulated and for the most part the tidal-frequency combinations employed were not those that the body naturally chooses (cf. figs. 8 and 9). It is perhaps of significance that the highest calculated efficiency appears for the condition (30 l/min. at a frequency of 20) that most closely corresponds to a naturally occurring one. This suggests that the respiratory apparatus may be so designed that the

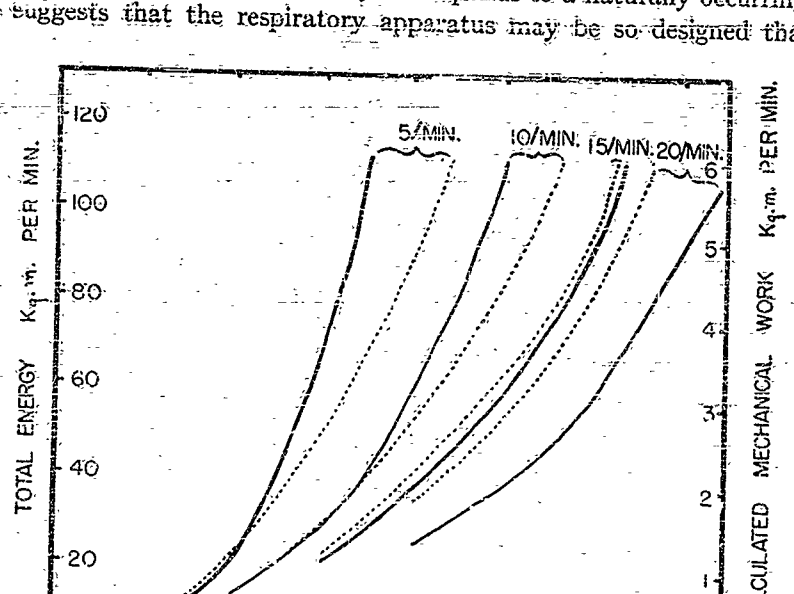

Fig. 9. WORK OF BREATHING at different ventilations and frequencies of breathing. *Left-hand scale of ordinates* refers to solid lines which represent total energy turnover as obtained by conversion of Liljestrand's (11) data for extra oxygen consumption. *Right-hand scale* refers to dotted lines which represent mechanical work calculated from *equation 11*.

conditions for minimal mechanical work are also those for maximal muscular efficiency.

At any rate it would seem that although 5 per cent is a representative efficiency for a considerable range of frequency-tidal combinations, the breathing under normal conditions of regulation may be usually carried out with a higher efficiency, in the order of 8 to 10 per cent.

It might be supposed that the relatively low mechanical efficiency of respiration could be attributed to insufficient opportunity for shortening of the intercostal muscles. Since they are arranged parallel to the circumference of the chest it might be supposed that they would have difficulty in shortening

when the chest expands. Actually they are attached to the ribs in such a way that they can shorten an appreciable fraction of their length like any other muscles in the body. It is a general rule that muscles can shorten *in situ* only 50 per cent of the length of the individual fibers and the muscles of respiration are no exception in this espect. Isolated frog muscles, when stimulated, usually shorten, with no load, about one third of their resting length, and give maximal work and maximal efficiency when the load is such as to reduce this shortening to about one sixth. From this point of view, the muscles of respiration must operate under fairly efficient mechanical circumstances.

Maximal Work Obtainable from the Muscles of Breathing. The mechanical work done in the usual resting breathing may be estimated from figure 7 as being in the order of 0.4 to 0.5 kilogram meters per minute. Assuming an efficiency of 5 per cent this corresponds to a total energy requirement of about 0.0234 large calories per minute or 33.7 large calories per day. This amounts to only 1 or 2 per cent of the total resting metabolism; the fuel requirement for 24 hours of quiet breathing is only 10 grams of sugar, a fraction of a candy bar.

For comparison, it is interesting to estimate the maximal work output that can be obtained when the breathing system is operated at full capacity. This estimate may be made by three independent methods, which will now be described.

The maximal ventilation that an individual can perform is in the order of 150 liters per minute carried out at a frequency of 30 per minute. Under these conditions expiration can not be entirely passive, but if one assumes that the same amount of viscous and turbulent resistance must be overcome during expiration as during inspiration, and that the elastic energy stored during inspiration is available to aid expiration then inspiratory work rate can be calculated by *equation 11* and expiratory work rate by:

Rate of expiratory work =

$$\tfrac{1}{4}K'\pi^2(fV_T)^2 + \tfrac{2}{3}K''\pi^2(fV_T)^3 - \tfrac{1}{2}KfV_T^2 \qquad (15)$$

The total work per unit time is the sum of *equations 11* and *15*, or

Work rate =

$$\tfrac{1}{2}K'\pi^2(fV_T)^2 + \tfrac{4}{3}K''\pi^2(fV_T)^3 \qquad (16)$$

By *equation 16* it is calculated that the mechanical work required for maximal ventilation is 270 kilogram meters per minute or 9.0 kilogram meters per breath.

Another approach is to estimate the potential energy available for maximal inspiration and expiration from figure 1 of Rahn, Otis, Chadwick and Fenn (8) which shows the maximal inspiratory and expiratory forces available at various lung volumes. The total area bounded by the curves for these maximal forces gives the theoretical maximal work available during a single cycle con-

sisting of a maximal inspiration and expiration. This method yields an estimate of 10.4 kilogram meters.

The maximal muscular forces available may also be estimated from anatomical data relating to the length, cross sectional area, and degree of shortening of the respiratory muscles. According to von Ebener (14) the lengths of the external and internal intercostals are 1.3 cm. and 1.6 cm. respectively, and in a full inflation or deflation of the chest the degree of shortening is about one eighth to one fourth of the muscle length for the former and one third to one half for the latter. The total cross sectional area of all the internal intercostals on one side of the chest is given by Weber, cited from Strasser (15, p. 143) as 97 $cm.^2$, and the corresponding figure for the external intercostals is 47 cm^2. Taking the force of contraction of these muscles as being similar to that for other human muscles (about 10 kg/cm^2 cross section) we have calculated the maximal work and entered the value in table 3, where the estimates by the other two methods are shown for comparison.

The value from the area of the *P-V* diagram is probably the most reliable

TABLE 3. MAXIMAL WORK AVAILABLE FOR BREATHING

METHOD OF ESTIMATION	WORK/BREATH	WORK/MIN. AT 30 BREATHS/MIN.
	kg. m.	*kg. m.*
Equation 16	9.0	270
Area of P-V diagram	10.4	312
Anatomical data	8.0 — 13.5	240 — 405

since it is based on actual measurements on 15 individuals. The estimate by *equation 16* is of course a large extrapolation from rather scanty data and involves numerous assumptions. The calculation from the anatomical data must also be considered as only approximate. The work of the diaphragm is omitted from this calculation because we do not have the necessary data.

Considering the admittedly rough methods involved, the similarity of these values is quite gratifying and gives one confidence that the estimates are at least of the correct order of magnitude.

It is interesting to note that although the maximal ventilation is only about 15 to 20 times the resting ventilation, the rate of work required is about 500 times greater for the former. Of course, this maximal work output can be kept up for only short periods of time, but the margin of safety provided for emergencies is impressively large.

COMMENT

The above presentation should be regarded as only an approximate overall picture of the respiratory apparatus considered from the mechanical point

of view along the lines sketched by Rohrer (3). Experimentally, the most inexactly estimated factor is probably the value for the non-elastic resistance of tissue since this determination was based on the assumption that the subjects were able voluntarily to relax completely and to permit the respirator to do all the work. Complete passivity is most likely not attained under these conditions, and the overlapping of the two sets of data shown in figures 3 and 5 is probably in part a manifestation of this inability to relax completely. Wirz (16) was able to describe the non-elastic resistance of the dog lung by an equation of the same form as our *equation 4* but he obtained negative values for the constant k_4. According to Bayliss and Robertson (6) and Dean and Visscher (7) at least a part of the non-elastic resistance of the lung is independent of velocity. For these various reasons we do not have confidence in the actual values obtained in our evaluation of non-elastic resistance of tissue. It seems likely, however, that we may have overestimated rather than underestimated the magnitude of this factor.

The approach employed in this analysis of the work of breathing, with emphasis on energy relationships and efficiency, is not to be justified so much by the importance of the magnitude of the work, which is generally relatively small, but rather as an aid in clarifying the interrelationship of some of the various factors involved.

In a more detailed analysis many factors would have to be included that are here omitted. For example, there is now good evidence that ventilation to various parts of the lungs is unequal (17, 18). It is also recognized that for optimal conditions of gas exchange a certain relationship should be maintained between blood flow and ventilation (19, 20). Since the breathing apparatus is a blood pump as well as an air pump, it may play an important part in the regulation of this ventilation/blood flow ratio. Certain patterns of breathing may be more efficient than others in this regard, and the selection by the body of particular tidal-frequency combinations may be related to this function.

Further study of respiratory mechanics should include investigation of the more detailed behavior of the respiratory muscles, their sequence of contraction and the behavior of the lungs in producing inequalities of ventilation. The work done by the breathing apparatus in moving blood as well as air should be evaluated, and the relationship between the pattern of air flow and that of blood flow should be considered.

SUMMARY

Relaxed human subjects were ventilated by a Drinker respirator while the velocity of respired gas flow and the pressure gradient between the mouth of the subject and the inside of the respirator were continuously and simultaneously recorded. From such experiments elastic resistance and total resistance to breathing were estimated. Resistance related to moving gas through

the respiratory tract was measured on the same subjects by the method of interruptions. From the experimental data equations are derived that give an approximate description of the human breathing apparatus as a mechanical system. These equations permit the estimation of the work of breathing under various conditions, optimal frequencies of breathing, maximal mechanical work output of the respiratory muscles, and mechanical efficiency.

The authors wish to acknowledge the cooperation of Dr. Donald Proctor in some of the preliminary experiments and to thank Mr. William Doherty for technical assistance.

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Mechanics of Respiration

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THE mechanics of breathing is a problem requiring on one hand the detailed knowledge of a classical anatomist and on the other hand the analytic understanding of an engineer. The anatomists have clearly presented their side of the subject and their conclusions have duly penetrated to the pages of current textbooks. It is amazing, however, to discover how superficial has been the analysis of the engineering aspects of the subject by physiologists. Perhaps it is because, to most physiologists, chemistry has seemed a more fruitful tool than physics; or more likely because the flow of air through tubes seemed too simple for serious attention or of too little practical value to medicine. Be that as it may, this chapter will strive to present an analysis of the problem from the point of view of an engineer who may wish to know for the breathing machinery of man the stresses and strains, limiting factors, reserves, power loads and work loads. No two men are the same and it will be necessary to use average values where they are available and individual values where averages are lacking. However, the methods are applicable to abnormal as well as to normal individuals and an accurate scientific description of an individual breathing apparatus can hardly fail to have practical value.

One of the first pieces of information which an engineer would wish to have concerning any pump is the stress-strain or the pressure-volume diagram. This is given in Figure 1 for the human chest and lungs (Rahn et al. 1946). Volumes in per cent of the vital capacity are plotted vertically while pressures, positive and negative, are plotted horizontally.

Maximum Inspiratory and Expiratory Pressures. The outer boundaries of the diagram are formed by the maximum inspiratory and expiratory pressures which can be exerted at different lung volumes. The pressures are measured simply by expiring and inspiring with maximum effort against a mercury manometer with care to avoid the use of the cheeks in blowing or the tongue in sucking. The corresponding volume is measured from a recording spirometer in the breathing circuit using as a reference point the relaxation volume, Vr, which is reached at the end of a normal passive expiration. After reaching the desired volume the subject is switched from the spirometer to the manometer and the resulting maximum inspiratory or expiratory pressure is recorded. The pressure produced is read from the manometer and is plotted against the final volume of the lungs at the time when the pressure is developed. For positive pressures this volume is slightly less than the volume calculated from the spirometer because the pressure compresses all the air in the lung including the residual air. Thus starting from the point of maximum inspiration at zero pressure (Y = 100, X = 0) in Figure 1, pressure is exerted along the slightly curved line represented by the arrow to the right. Similarly, starting from the point of maximum expiration at ambient pressure (Y = 0, X = 0), inspiratory pressure is exerted to the left along the slightly rising arrow. This arrow slopes less than the one for positive pressures because the total lung volume is confined to the residual

air and does not include also the vital capacity.

These curves for maximum inspiratory and expiratory pressures outline the total range of pressures and volumes which can be concerned in any respiratory maneuver.

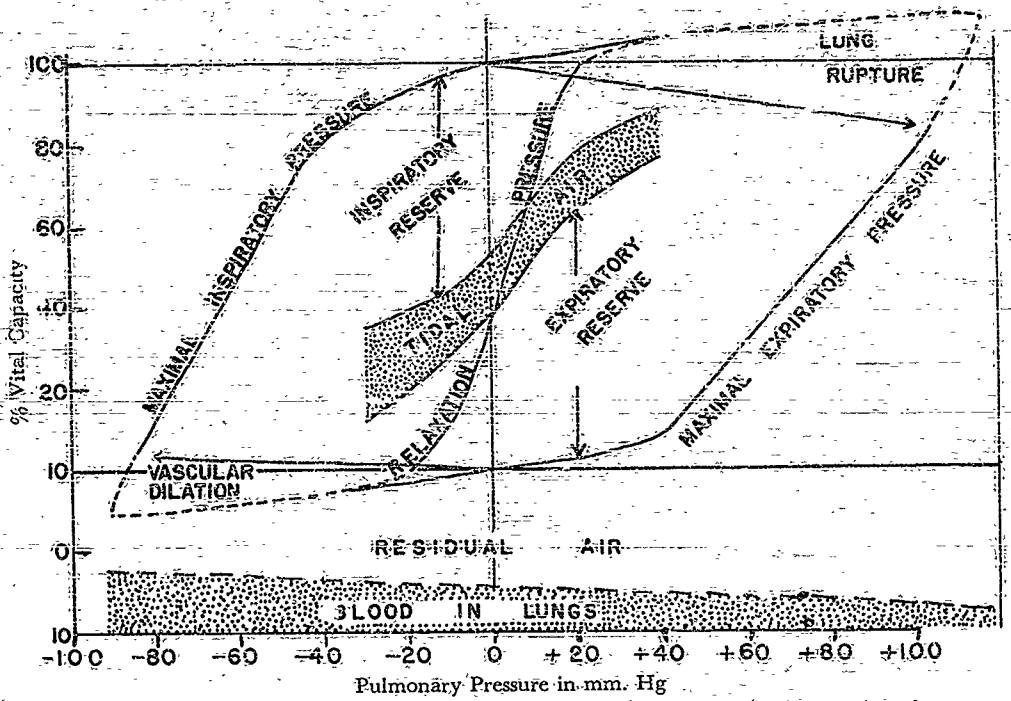

FIG. 1. Pressure-volume diagram of the human chest, after data of Rahn et al. (1946).

No pressures greater than this can be attained either positive or negative unless this is done by artificial means. The right side of the diagram at relatively low pressures is the area concerned in continuous pressure breathing for therapy or intermittent pressure breathing for artificial respiration. At higher pressures of 40 to 50 mm. Hg air may begin to leak through the connective tissue of the bronchioles and penetrate through the mediastinum to produce interstitial emphysema in the neck or abdomen (Katz, 1909; Kronecker, 1909). At still higher pressures of 60 to 100 mm. Hg (Henry, 1945) the lungs are likely to rupture. The dotted line, representing expiratory pressures on the right side of the chart are unexplored because of this danger of damage to the lungs. Accidents have occurred in this region in sailors practicing submarine escape technics (Polack and Adams, 1932). If the breath is held during the ascent, the pressure rises to dangerous levels and may force air into the blood vessels and cause cerebral emboli. Likewise in explosive decompression, which would result from sudden loss of cabin pressure in a stratosphere plane, the chest is maximally expanded until the excess air can escape.

In the process of defecation the pulmonary pressure may be very high but there is little strain on the lung because it is not markedly expanded. The negative side of the chart is concerned in all inspirations. Rather high relative negative pressures may be attained in subjects immersed in water and breathing ambient pressure through a tube reaching to the surface. In such an experiment the inspiratory pressure curve indicates the maximum depth at which inspiration is possible at all lung volumes According to the chart the maximum inspiratory pressure is about 80 mm. A recent study of this question (Mackay, 1948) has placed 5 feet of water as the limiting depth beyond which inspiration becomes impossi-

ble. This would correspond to about 112 mm. Hg. In such an experiment the pressure in the lungs is not negative relative to the atmospheric pressure but is negative relative to the pressure in the water surrounding the body, so that the differential effect is identical to that produced by the application of an equal negative pressure to the lungs. Extreme negative pressures, indicated by the dotted lines, have not been explored because of the danger of overdilating the blood vessels and the possibility of pulmonary hemorrhage. One experiment of this sort (Stigler, 1911) was reported to have resulted in a dilated heart.

Vital Capacity. Vertical distance at any point on the abscissas in Figure 1 between the inspiratory and expiratory pressure lines represents vital capacity. In theory, therefore, the diagram could have been obtained by measurements of vital capacity at different pressures although safety considerations would have limited the data to pressures of 40 mm. and less. It will be observed that small changes in pressure in either direction have little effect upon the vital capacity but at larger pressures, both positive and negative, the vital capacity diminishes and ultimately reaches zero at some undetermined point. Both the inspiratory and the expiratory pressure curves have been continued as solid lines for some distance beyond the line of zero pressure. Over this area vital capacities have been measured in thirteen normal individuals (Rahn, Otis, Chadwick and Fenn, 1946) and the lines drawn are in accord with the resultant findings. It is furthermore reasonable to expect that the volume of maximum inspiration can be somewhat increased when the subject is aided by some positive pressure in the lungs and vice versa. This effect is indicated in the chart.

Expiratory and Inspiratory Reserves. These fractions of the vital capacity are indicated in Figure 1. The expiratory reserve is the fraction between the end of a normal expiration and the point of maximum expiration. The inspiratory reserve is the volume between the end of a normal inspiration and the maximum inspiration at the same pressure. These terms are preferred to the former terms complemental and supplemental air because they are self-explanatory. They have been recommended for use by a committee on respiratory terminology which reported recently.*

Residual Air. It will be noticed in Figure 1 that the residual air varies markedly with pressure, being much greater at positive pressures and somewhat smaller at negative pressures. On the positive pressure side, this increase in residual air results chiefly from the inability of the expiratory muscles to deflate the chest to the usual degree against the positive pressure in the lungs. A further factor of minor importance is the variation in the amount of blood in the chest. This is diminished at positive pressure but increased at negative pressure. Such changes in the amount of blood cause corresponding changes in the space available for residual air. For this reason the lower boundary of the residual air in Figure 1 is not horizontal. The shaded area represents varying amounts of blood in the lungs. This part of the diagram is somewhat schematic because accurate data are not yet available. Present data indicate that 200 to 500 cc. of blood can be forced out of the lung by positive pressure (Fenn et al. 1947).

Relaxation Pressure Curve. The pressure-volume curve for passive inspiration and passive expiration is called the "relaxation pressure curve" (Rahn et al. 1946). This has an "S" shape as shown in Figure 1 and crosses the vertical axis at Vr, which is the relaxation volume at ambient pressure and corresponds to the end of a normal expiration. The stippled area marks the position of the tidal air while breathing voluntarily at different positive and negative pressures. The relations between these two can be described after a further account of the relaxation pressure curve has been given.

Relaxation pressure curves can be obtained by two different methods: (1) by measuring volume changes resulting from different pressures and (2) by measuring pressure changes occurring at different volumes.

* *Federation Proc.*, 9: 602, 1950.

The first of these methods was utilized by Jaquet in 1908 and Bernoulli in 1911 who were the first to obtain curves of this type. The subjects were in a closed chamber breathing through a tube held in the mouth and connected to a spirometer outside of the chamber. Rhythmical variations in pressure were applied to the interior of the chamber causing rhythmical inflations and deflations of the chest which were recorded on the spirometer. Therefore, this represents an early application of the principle of the Drinker respirator. By varying th pressures in steps of 15 mm. Hg from −40 to +40 mm. Bernoulli was able to plot the whole resting pressure-volume diagram.

As a second method, similar data may be secured by voluntarily inflating the chest to a known value, starting from the point of complete relaxation then connecting the lungs to a manometer by a tube inserted in one of the external nares (Rahn et al. 1946). When the inflated chest relaxes a positive pressure is developed. If the chest is first deflated by a forceful expiration, a negative pressure is developed in the manometer when the muscles are relaxed. From this procedure the curve derives its name of relaxation-pressure curve. No careful comparison has ever been made between the curves obtained by these two different methods but presumably they would be identical if the respiratory muscles are completely and equally relaxed in both cases. The curve is useful in showing the pressures which would have to be applied by an artificial respiration apparatus in order to produce any desired change in volume or any desired tidal air.

The most complete data on relaxation pressures are those of Rahn et al., 1946, from data on fourteen subjects. Over the normal physiologic range the slope was found to be 94 cc. per mm. Hg. For experimental purposes the elastic characteristics of the chest can, therefore, be simulated by the use of a rigid chamber of 7 l. capacity since the addition of 94 cc. of air will raise the pressure by 1 mm. as in the human lung. There are considerable differences in this slope in different individuals but there has been no study which permits any correlation between this slope and any other characteristics of the individual such as age or body weight.

The effect of posture on the relaxation pressure curve was first studied in a single subject by Rohrer (1916, 1925) who found that it was shifted to the right (Fig. 3) when the posture was changed from the erect to the supine position. A still further shift in the same direction was produced by the head-down position. These data were largely confirmed by Rahn et al., 1946, although there seemed to be no change at the larger lung volumes in their data. As an average value in thirteen men it was found that the relaxation pressure at the end of a normal expiration increased 7.5 mm. Hg when the position was changed from the erect to the supine position. This is about equal to the average pressure over the diaphragm due to the fluid abdominal contents in the supine position if the diameter of the thorax is considered to be 20 cm. The change in the relaxation pressure curve, therefore, is presumably due to the weight of the viscera.

Tidal Air. The tidal air band in Figure 1 shows the lung volumes which are instinctively selected when breathing against different positive and negative pressures (Rahn et al. 1946). It is evident that at ambient pressure the lower edge of the tidal air band coincides with the relaxation pressure curve. This means that expiration is passive. At a positive pressure of 9 mm. Hg it is the upper or inspiratory edge of the tidal air which becomes the point of relaxation. At this point inspiration becomes entirely passive while expiration is active. With still higher pressures the chest never comes to rest throughout the breathing cycle but the subject continuously exerts some expiratory pressure even at the height of inspiration. When breathing against negative pressures, likewise, there is no point of relaxation but in this case a continuous inspiratory pressure is exerted to prevent the chest from collapsing.

Lung Elasticity and Chest Elasticity. The

relaxation pressure curve can be further analyzed into its two components, that due to the elasticity of the lung and that due to all the other elastic structures in the chest including the diaphragm, the chest walls and the abdominal wall. This is illustrated by the curves in Figure 2 where a relaxation pressure curve is plotted as a solid line and the probable pressure-volume diagrams of the lung and the chest (including the diaphragm, etc.) as dotted lines. At the relaxation volume, Vr, the pressures exerted by the chest and the lungs are equal and opposite. The chest tends to expand with a pressure equal to the collapsing pressure of the lungs. At a volume of about 53 per cent of the vital capacity the chest attains its resting position, this being the point where the P-V curve of the chest crosses the Y axis.* At the same volume the lung elasticity curve crosses the relaxation pressure curve. At this point all of the relaxation pressure is due to the lung elasticity. In a pneumothorax when the lung collapses the chest should expand to its resting point.

Since the lung is always tending to pull away from the chest, there is potentially a negative pressure between the lung and the chest in the intrapleural "space." Because of this negative pressure it might be anticipated that gas bubbles would tend to accumulate until an actual space appears. That this does not happen is due to the peculiar shape of the oxygen dissociation curve. According to this curve the fall in oxygen pressure caused by the removal of a given volume of oxygen from the arterial blood is far greater than the rise of carbon dioxide tension caused by the addition of an approximately equal amount of carbon dioxide. For this reason the sum of the tensions of the dissolved gases in the venous blood and the tissues generally is always less than that in the arterial blood and less than the total pressure in any bubble inserted into the intrapleural space. The bubble is, therefore, absorbed because the partial pressures of the gases are always less in the tissues than they are in the bubble. It is not always realized that the whole

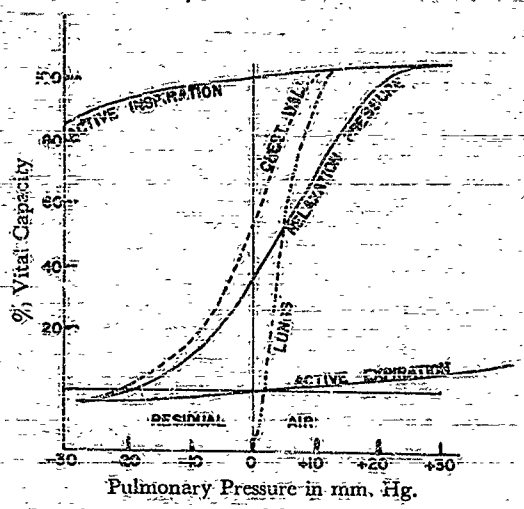

FIG. 2. Relaxation pressure curve (solid line)—average data from fourteen subjects of Rahn *et al.* (1946). Dotted lines represent best guess as to the pressure-volume curves of the passive chest and lung separately. Portions of the active pressure-volume curves are also shown.

mechanism of breathing by the lungs would be impossible if it were not for this remarkable mechanism. It is the same mechanism, of course, which causes the absorption of gas in an artificial pneumothorax. One cannot help wondering naively whether this particular advantage of the shape of the oxygen dissociation curve of blood was "realized" when the human breathing mechanism was first "invented." Without it, however, the whole "machine" would have been a failure.

The pressure volume curve of the isolated lung was first measured by Liebermeister (1907) on one lobe of a human lung removed immediately after death from an executed criminal. He found that lungs from autopsies gave erratic results. A very similar curve for a dog lung is shown in Figure 3 from the work of Romanoff (1910). The "S" shape of this curve has more recently been confirmed by Lawton and King (1949) who pointed out the resem-

*This crossing was previously taken to be at 72 per cent of the vital capacity because the emphysematous chest expands to that degree, presumably due to loss of lung elasticity (Rahn et al. 1946). There may, however, be other changes in emphysema in addition to those in the lung itself and the new value of 53 per cent fits better with new concepts concerning the S-shape of the lung elasticity curve.

blance to the P-V curve obtained from a rubber bag. According to the theory of extensibility of rubber there should be a middle portion of high extensibility where the arrangement of the chain molecules becomes less random and the entropy

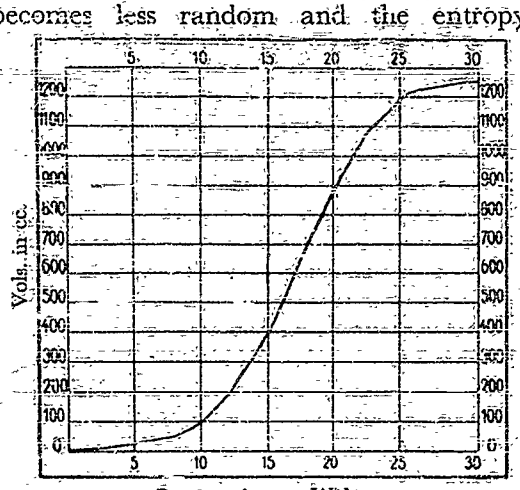

FIG. 3. Pressure-volume curve of a dog-lung, from Romanoff (1910).

decreases as the volume increases. At smaller volumes greater resistance to expansion is offered by molecular forces and at larger volumes the rubber stiffens because of a sort of crystallization process (King and Lawton, 1950). Although this simple explanation seems quite adequate, some anatomic factors might also be involved. Be that as it may, over the physiologic range the expansion of the lung seems to be a linear function of the volume (Cloetta, 1913). The expansion of the lung per mm. Hg over this range is 27 per cent of the vital capacity according to Liebermeister (1907) and probably 16 per cent for laboratory animals according to Romanoff (1910). The uncertainty in the latter case is due to lack of precise information as to the fraction of the curve (Fig. 3) which can be assigned to the vital capacity (900 cc. has been assumed). The steepest part of the lung elasticity curve of Figure 2 has a slope of about 15 per cent per mm. Hg.

The lung elasticity can be measured *in vivo* by recording the intrapleural pressure during quiet breathing at different tidal volumes. Such records were first adequately studied by Neergaard and Wirz (1927) who pointed out that the elasticity of the lung could be measured at the points where the velocity of air movement was zero, i.e., at the points where the direction of flow was reversing. While air is moving or the lungs

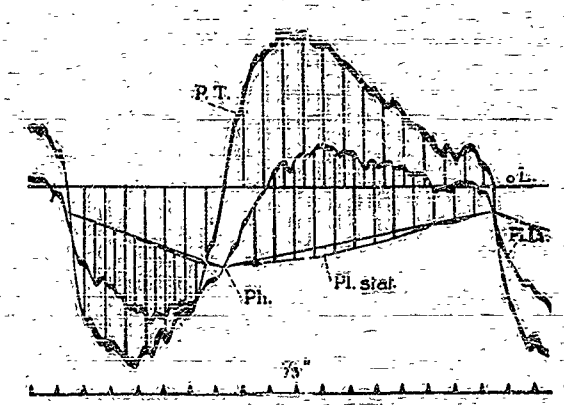

FIG. 4. Intrapleural pressures (Pl. Dr.) in an emphysematous patient and simultaneous record of the velocity of flow (PT = pneumotachogram), from Neergaard and Wirz (1927).

are expanding, there are pressure differences caused by the pressure gradient required to move the air either in or out and the pressure required to deform the lungs. A record of intrathoracic pressure coupled with a record of the velocity of flow of the air permits a measure of both lung elasticity and the resistance to movement. A typical record is shown in Figure 4 in which P.T. represents the pneumotachogram and Pl.Dr. the intrapleural pressure record. The value Pl.Dr. at points where P.T. crosses the zero line (oL.), as for example Ph, is a measure of the lung elasticity. The line Pl. stat., therefore, represents the static elastic pressure. Deviations from this value are due chiefly to the pressure required to move the air.

Values for the lung elasticity can also be approximated indirectly by simultaneous measurements of the venous pressure, pulmonary pressure and pulmonary volume. This method is based upon the assumption that changes in the intrapleural pressure are reflected by equal changes in the venous pressure. This is more nearly true of the right auricular pressure but even the pe-

ripheral venous pressure follows the intrapleural pressure, qualitatively at least, but with a slight lag depending upon the rate of blood flow. So long as the lung volume remains constant, an increase in pulmonary pressure results in an equal increase in venous pressure. If, however, the lung is allowed to expand when pressure is applied to the trachea, only a fraction of the applied pressure appears as an increase in the venous or the intrapleural pressure because some of the applied pressure is absorbed in the elastic walls of the lungs. Under normal conditions about half of the applied pressure is passed on to the intrapleural space or to the venous blood. Proceeding in this way Otis, Rahn and Fenn (1946) obtained a value for the extensibility of the lung of about 5.7 per cent of the vital capacity per mm. Hg. This agreed with a similar estimate by Rohrer (1915) and was even higher than estimates by Neergaard and Wirz (1927) and Christie and McIntosh (1934). This value fits well with the suggestion that the expansion of the chest to 72 per cent of the vital capacity in emphysema is due to complete loss of lung elasticity but it does not accord with an "S"-shape curve for lung elasticity (Lawton and King, 1949) and is probably too low. Therefore, it is possible that other factors contribute to the expansion of the emphysematous chest. Figure 2 is drawn with the steeper lung elasticity slope and the "S"-shaped curve but its correct position is not well established.

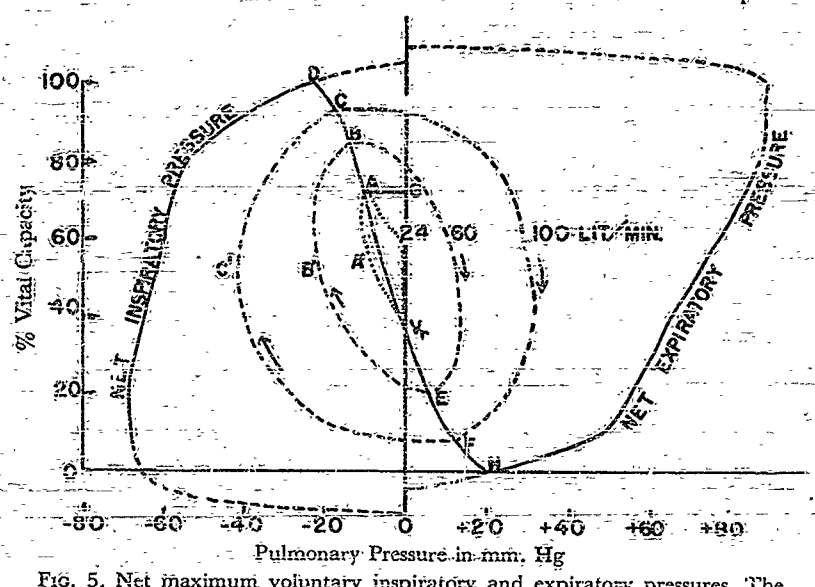

FIG. 5. Net maximum voluntary inspiratory and expiratory pressures. The pressures required to balance the relaxation pressures are indicated by line HD. Three respiratory loops for three different ventilation rates (as indicated) are represented by dotted lines A', B' and C'. Areas of these loops represent the work required for these ventilation rates.

Net Voluntary Pressures. The maximum pressure recorded at each volume in Figure 1 represents the algebraic sum of passive and active pressures. The net pressure produced by the contraction of the respiratory muscles is obtained by subtracting the relaxation pressures from the maximum voluntary inspiratory and expiratory pressures at every volume. The outer curves plotted in Figure 5 represent these differences. A mirror image of the relaxation pressure curve of Figure 1 is also plotted in Figure 5. In this case it represents the inspiratory or expiratory force which must be exerted in order to balance the relaxation pressure and so produce corresponding increases or decreases in the volume of the chest.

The area between the relaxation pressure curve and the Y axis represents the elastic work required to inflate or deflate the chest,

starting from the relaxation volume Vr. This is the work which would actually be required if the change in volume occurred so slowly that frictional resistance was negligible. In ordinary breathing this is not the case and the dotted line VrA'A represents the pressures actually required in increasing the volume 1.6 L. from Vr to G at a frequency of 15 per minute. The total work done during this inspiration is VrA'AG. During expiration the potential energy VrAG is available to accomplish the work of expiration. In this case the potential energy stored in inspiration is more than sufficient for expiration since the expiratory loop (indicated by the dotted line to the right of VrA) is entirely covered by the triangle VrAG. This is no longer the case at higher ventilation rates as indicated by the two other respiratory loops for 60 and 100 L. per minute as shown in Figure 5. To the extent that these loops overlap to the expiratory side of the diagram it will be necessary to make use of active expiratory effort to accomplish the ventilation required. It is interesting to note what a small fraction of the total area of the pressure volume diagram is required for normal breathing, only about 0.3 per cent. Even in breathing at the high rate of 100 L. per minute (FC'C) only about one-third of the total is needed. If the subject could increase his tidal volume, however, to 100 per cent or 4.7 L. and his frequency to 30 per minute the calculated work becomes 7.1 kg.m. while the total area of the PV diagram is 8.7 kg.m. This, of course, does not prove that an individual represented by the diagram of Figure 5 should be able to breathe at the high rate of 4.7 × 30 or 141 L. per minute. The rate with which he can bring his reserve forces into play is a limiting factor as well as the actual magnitude of these forces.

This discussion has provided an over-all picture of the work of breathing and its relation to the total energy available. It is necessary now to indicate how these respiratory loops were calculated or measured and to describe how the different fractions of the respiratory work are evaluated.

Measurement of Work of Respiration in Drinker Respirator. The respiratory loop VrA'A in Figure 5 was measured by placing a subject in a Drinker respirator and providing passive ventilation. The subject was instructed to relax as completely as possible and to permit the machine to ventilate his lungs without any effort on his part. The pressure inside the respirator was continuously recorded. The velocity of the air which passed in and out through the mouthpiece was recorded at the same time by means of a pneumotachogram or flowmeter. The volume of the chest was determined by integration of the flow curve at successive points. As an alternative, and for this purpose a simpler method, a subject could have breathed in and out of a recording spirometer. If the pressures in the respirator are plotted against the simultaneous volumes on the spirometer, measured from the relaxation volume, Vr, as a base line, the loop VrA'A is the result. To produce this same rate of breathing voluntarily the muscles will have to exert a pressure equal to that provided by the respirator. In this case the total work of the respiratory cycle is not the area of the loop alone but rather the slightly larger area VrA'AG. That part of the potential energy VrAC which was not needed for moving the air, i.e., the area outside the loop, represents energy used in working against the air pressure in the machine during expiration.

The other respiratory loops in Figure 5 are only diagrammatic but their total areas were determined by calculation in a manner to be described later.

Theoretic Resistance to Air Flow. The resistance of the airway was studied by Rohrer in 1905 (cf. also 1925) in an exhaustive manner. It is extraordinary that so little attention has been paid to this admirable contribution. He measured carefully the lengths and the diameters of the various sections of the air way and calculated the resistance of the whole system. The equation which he arrived at on theoretic grounds came very close to the value determined later experimentally.

For the most part the flow of air is laminar or streamlined rather than turbulent. For laminar flow the pressure drop, p, required for a given velocity of flow, v, is given according to Poiseuille's law by the equation (Equation 1):

$$p = \frac{8l.v.\eta}{981.r^2} = \frac{kV}{r^4}$$

where p is in cm. of H_2O, v is in cm. per sec., r is the radius in in., l is the length in cm. and η is the viscosity which in absolute units equals 0.0001873. V is the volume flow in liters per second and k is a constant.

When the velocity, v, exceeds a critical value, the flow becomes turbulent and the pressure drop varies as v^n where n has a value between 1.7 and 2.0. The critical velocity (in cm. per sec.) for turbulent flow equals

$$\frac{1290\eta}{d\gamma} = \frac{216}{d}$$

where η is the viscosity, γ the density of air (relative to water) and d is the diameter in mm. For the human trachea with a diameter of 21 mm. the critical velocity is 10.3 m./sec. or 216 L./sec. which is far in excess of any velocity attainable except perhaps momentarily in a cough. The velocity of air flow in the different parts of the airway (relative to the tracheal velocity as 1.0) is 3.39 in the glottis, 1.70 at the nasal openings; it reaches a second maximum of 1.64 in the bronchioles of 6 mm. diameter and diminishes to zero with some minor fluctuations in the smallest alveolar ducts. There is little likelihood, therefore, of exceeding the critical velocity anywhere in the airway. Turbulence does develop, however, for other reasons when the air changes direction rapidly as in the nasopharynx or when the diameter of the air way is abruptly altered as it is at the glottis. The pressure drop at all such points increases as the square of the velocity. The complete equation (Equation 2), therefore, for the pressure drop is:

$$p = 0.79V + 0.801V^2$$

where p is in cm. H_2O and V is L./second. Here the first term is for streamline resistance (as in Equation 1) and the second for turbulent resistance at particular points in the airway. The division of the resistance between the upper airway (trachea and above) and the lower airway or bronchopulmonary systems can be deduced from the following equations from Rohrer:

Upper airway $p = 0.426V + 0.7135V^2$
Lower airway $p = 0.364V + 0.0875V^2$

The turbulent fraction is, therefore, far greater in the upper airway and increases rapidly with the velocity.

Rohrer estimates that when the rate of ventilation increases from 6 to 60 L./minute, the percentage of the total resistance which is due to turbulence increases from 10 to 50 per cent. In both cases, however, nine-tenths of the turbulence occurs above the trachea. The fraction of the total resistance which occurs above the trachea is 58 per cent at 6 L./minute and 71 per cent at 60 L./minute. While more than half of the total resistance to breathing is located above the trachea in the larger passages, it is interesting that below the trachea the resistance increases as the vessels become smaller. In the ultimate lobules Rohrer estimates that the tubes branch dichotomously in such a way that each branch is 0.82 as long and 0.82 as wide as the parent tube. At each branching, therefore, the resistance per unit of length increases

$$\frac{1}{2.r^4} = \frac{1}{2 \times 0.82^4} = 1.1 \text{ times.}$$

When the smallest passages become partially obstructed by the accumulation of fluid, turbulence does develop and is recognized by the diagnostician as rales in the stethoscope. Turbulence is also produced at the glottis when the vocal cords are still further approximated and results in phonation.

Measurement of Resistance to Air Flow. A method of verifying Rohrer's equation was provided by the suggestion of Vuilleumier that the pressure gradient between the mouth and the alveoli could be measured

by the intermittent interruption of the flow. This method was taken up in the writer's laboratory by Otis and Proctor (1948) who confirmed the equation but obtained somewhat different values for the constants. The method consists in momentarily interrupting the flow of air during quiet breathing by closing a slide across the breathing tube. The slide is actuated by a solenoid and is returned to its original position in a fraction of a second by a strong spring. The brief interruption of the breathing is not perceptible to the subject. Simultaneous measurements are made of the pressure between the shutter and the lungs and the rate of flow as indicated by a flowmeter on the "far" side of the shutter. When the flow of air is interrupted during inspiration, the flow record goes to zero and the pressure at the mouth falls to a value which is nearly equal to the low pressure existing in the relatively large volume of the alveolar air at that instant. The change in pressure at the mouth indicates, therefore, the pressure gradient required to cause air to flow at the velocity recorded immediately prior to the interruption. When these pressures are plotted against the corresponding velocities, curves like those in Figure 6 are obtained. The slope of this curve may be taken as a measure of the resistance of the airway. The method lacks something of precision and the points scatter rather widely but the average can be described by the equation (Equation 3):

$$P = 3.5V + 1.5V^2$$

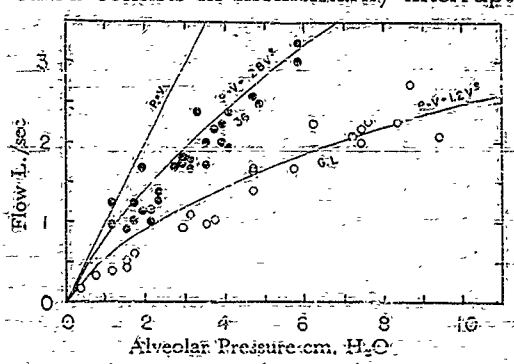

Fig. 6. The velocity of flow as a function of the pressure gradient in a subject breathing at ground level (G. L.) and at 36,000 feet simulated altitude. (From Otis and Bembower 1949.)

where P is in cm. of H_2O and V is in L./second.

The values of these constants have been studied at high altitudes and in helium breathing by Otis and Bembower (1949). One of their graphs for an individual breathing at ground level (G.L.) and at 36,000 feet simulated altitude is shown in Figure 6. The purely viscous resistance to laminar flow is shown by the curve P = V. The addition of the turbulent factor KV^2 is shown by the deviations of the experimental curves from this straight line. Since normal breathing is at the peak rate of about 0.3 L./second, it is evident that for the most part these curves describe relatively high rates of ventilation. The substitution of helium for nitrogen in breathing at ground level changes the density of the gas and provides a curve very similar to that given in Figure 6 for high altitudes. The change in density is about the same in each case and only the turbulence factor is affected. This explanation for the effect of helium on the breathing was also provided by Dean and Visscher (1941).

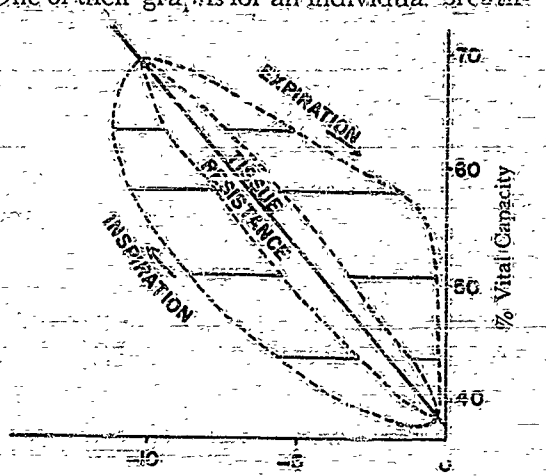

Fig. 7. A respiratory loop on the pressure-volume diagram obtained by passive ventilation in a Drinker respirator. Simultaneous values of pressure and volume provide the dotted lines. The solid diagonal is the relaxation pressure curve. (Redrawn from Otis, Fenn and Rahn 1950.)

With this equation for air flow available it is possible to pursue further the analysis of the work of breathing as measured on the Drinker respirator in a passive subject. In

this method continuous records are taken of the velocity of flow, V. Using these measured values of V for Equation 3 it is possible to calculate the corresponding pressure gradients which would be required. The result can be indicated in Figure 7 which shows an enlarged drawing of the respiratory loop VrA'A of Figure 5. These calculated flow gradients are laid off for both inspiration and expiration as horizontal lines at various points in the respiratory cycle. The area so marked out represents the work required to move the air and the remaining area in the middle of the loop represents work required to deform the tissues of the lung and chest, i.e., viscous work degraded to heat in those tissues. This work is presumably largely proportional to the velocity of movement but it has been empirically analyzed by Otis, Fenn and Rahn (1950) into two factors corresponding to the two terms of the air flow equation but with different constants. From data on three subjects by the respirator technic, Otis, Fenn and Rahn (1950) estimated for the work of inspiration at 15 per minute that 63 per cent was due to elastic forces, 28.5 per cent to air movement and 8.2 per cent to tissue resistance. Similar estimates based on artificial respiration of dogs by Bayliss and Robertson (1939) and Dean and Visscher (1941) attribute rather less to air resistance and more to the other two factors.

Calculation of Work of Breathing. The total pressure required for breathing is given by the equation (Equation 4):

$$P = KV + K'\left(\frac{dV}{dt}\right) + K''\left(\frac{dV}{dt}\right)^2$$

Here P is in cm. H_2O, t is in seconds and V is in L. The first term is the elastic pressure, the second the resistance due to viscosity and the third that due to turbulence. The constants K, K' and K'' have average values of 8.5, 3.5 and 1.5, respectively. If the velocity of air flow were constant throughout each phase of respiration, it would be easy to calculate the work of breathing by multiplying this force by the volume of air moved per second. Since, however, the velocity of flow varies, it is necessary to integrate the force over the whole volume change which occurs during the cycle. To do this some mathematical shape to the flow pattern must be assumed. One of the simplest assumptions is that the breathing follows a sine curve or $dV/dt = a \sin bt$ and $b/2\pi = f$, the frequency of breathing per second. Using these assumptions the following equation was arrived at for W, the mean total rate of work of inspiration (in kgm. cm. per sec.) with a tidal volume of V liters and a frequency of f breaths per second (Equation 5):

$$W = \frac{1}{2}fKV_T^2 + \frac{1}{4}K''\pi^2f^2V_T^2 + \frac{2}{3}K''\pi^2f^3V_T^3$$

Using this equation calculations have been made of the work required for the various ventilation volumes and frequencies used by Liljestrand (1918) in his measurements of the extra oxygen consumed for respiration. Both work and extra oxygen were converted into the same units and the ratio of the two values determined. This indicates that breathing is carried on with an efficiency of about 5 per cent.

Optimal Frequency for Breathing. For a given alveolar ventilation there must be a certain frequency of breathing which will require minimum work. If the frequency is too high, the tidal volumes are small and the dead space ventilation is a large fraction of the total. If, on the other hand, the frequency is too low, the tidals are too large. A large tidal volume is disadvantageous because the elastic work increases as the square of the tidal volume. This is evident because the elastic work of breathing is represented by the triangular area between the relaxation pressure curve and the Y axis. The area is equal to PV/2. But $P = KV$. Hence the work is $KV^2/2$. This is the first term of the work equation for inspiration (Equation 5). The optimum frequency for a given alveolar ventilation can readily be calculated if the tidal volume in Equation 5 be replaced by the Equation $V = A + d$ where A and d are the alveolar and the dead space fractions of the tidal volume. The

work equation is then multiplied through by f (no. of breaths per sec.) to obtain the work per second and the quantity Af is put equal to Va (the alveolar ventilation) and treated as a constant. This equation is then differentiated with respect to f and put

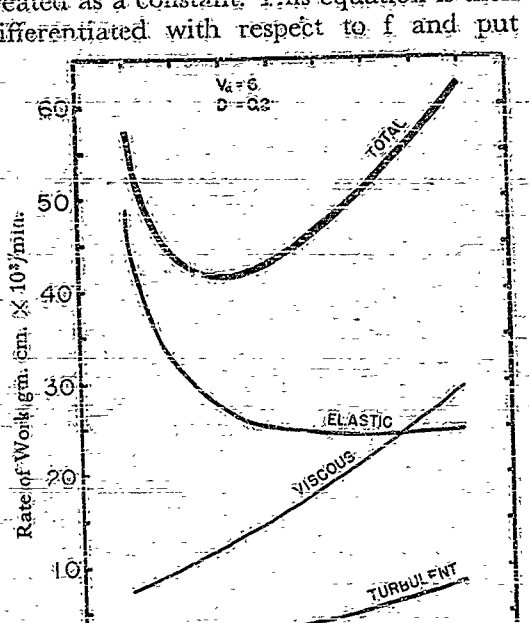

FIG. 8. Relationship of elastic, viscous and turbulent fractions of the total work of breathing at a rate of 6 L. per minute using different frequencies. Values calculated according to a modification of equation 5 after Otis, Fenn and Rahn 1950.

equal to zero to obtain the optimum. In this way it is found that for an alveolar ventilation of 6 L./minute the optimum frequency is 15 breaths per minute. For resting conditions, therefore, it appears that man instinctively chooses a frequency of breathing which is close to the point required for minimum work. From an economic point of view this may not seem very important because the total cost of breathing per day is covered by the energy derived from one candy bar or less; but the observation is perhaps important from a philosophic point of view. The principle of minimum work seems to govern most of the responses of living organisms.

It is instructive to plot out the values of the different fractions of the work of breathing as a function of frequency. This has been done according to the method outlined above and the result is shown in Figure 8. The curves represent the work required in the various categories to produce alveolar ventilation of 6 L./minute at the frequencies indicated. The total work is seen to pass through a minimum at a frequency of 15 as already mentioned. The elastic work steadily diminishes as the tidal volumes decrease or the frequency increases. The viscous and turbulent work fractions, however, tend to rise, the former as a linear function of the velocity and the latter as the square of the velocity in accordance with equation 3. At this alveolar ventilation volume of only 6 L./minute the turbulent factor is a small part of the total but at higher minute volumes it increases rapidly.

Equation 5 concerns only the work of inspiration and assumes that expiration is entirely passive. For relatively low rates of ventilation this is true. For higher minute volumes in which all of the elastic potential energy stored in inspiration is used for expiration, the total work for inspiration and expiration is equal to twice the value of the second and third terms of equation 5, without including the first term for elastic work at all. This is evidently true if the velocity pattern in expiration is the same as that in inspiration because, if the elastic work is added to the work of inspiration, it would have to be subtracted from the work of expiration. Derived in this way the total work per second is given by the following equation (Equation 6):

$$W = \frac{1}{2} K' \pi^2 f^2 V_T^2 + \frac{4}{3} K'' \pi^3 f^3 V_T^3$$

where W = kg.cm. per sec., f is breaths per sec., V_T is tidal volume in L. and K′ and K″ are constants with values of 3.5 and 1.5, respectively (for the three cases given by Otis et al. 1950). This equation was used for the calculation of the work areas of the respiratory loops in Figure 5 for ventilation rates of 60 and 100 L./minute. For such high ventilation rates equation 5 (for in-

spiration alone) would give too low values and conversely for low ventilation rates equation 6 would give too low values. It is apparently not possible to provide an equation which will cover adequately all rates of ventilation and for intermediate values it is necessary to try both equations and use the larger value.

Action of Respiratory Muscles. It may be pertinent to add one final word concerning the action of the respiratory muscles themselves. The total area of a pressure volume diagram represents the total work which could conceivably be performed by all of these muscles in transporting air in or out of the lungs. The muscles themselves, however, merely work by shortening under tension. When the external intercostals shorten, they cause the ribs to rise and the internal intercostals do the reverse. The area of the pressure volume diagram must eventually derive from the summation of the areas of all the length-tension diagrams of the individual muscles concerned in respiration. It has been possible from anatomic data in the older German literature to estimate the total cross sectional area of the intercostal muscles and the absolute amount of shortening which can occur between points of maximum inspiration and maximum expiration. Assuming that these muscles produce the same force per square cm. of cross section area as do other skeletal muscles when maximally innervated, it is possible to calculate the total work which they could conceivably perform. This would be the product of the total force by the maximum amount of shortening. It is interesting to find that this method predicts an area of the pressure volume curve which is between 8 and 13.5 kg.m. The actual area of the pressure volume diagram in Figure 5 was 8.7 kg.m. The contribution of accessory muscles of respiration, particularly the diaphragm, is omitted from these estimates but the agreement is surprisingly good.

These considerations reveal also the fact that the respiratory muscles are able to shorten by an appreciable fraction of their own length. This is necessary for the efficient performance of work. If they shorten too much, the tension is too low and if they shorten too little the work performed is too small. Their working conditions for respiration are evidently no less advantageous than those of other skeletal muscles.

SUMMARY

This outline of the mechanics of breathing is not altogether new and is largely a summary of recent work on the subject from the author's laboratory. The data apply primarily to normal healthy young males and the variations to be expected in other age groups and in clinical practice are still unknown. The outline is unsatisfactory also because of inadequate information concerning the elasticity of the human lung and its proper position on the pressure-volume diagram. No attempt has been made to deal separately with abdominal and thoracic types of breathing and indeed the data for this purpose are non-existent. The distribution of resistance to air flow between the upper and lower respiratory passages is not well documented experimentally and would be of much clinical interest. At best, an outline of the mechanical problems of breathing has been sketched and some possible methods of attack have been suggested for future additions to our knowledge of the subject.

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MEASUREMENT OF ALVEOLAR PRESSURE IN HUMAN SUBJECTS

A. B. OTIS AND D. F. PROCTOR

The resistance offered by the respiratory tract to air flow is an important factor in the work of breathing. However, there are relatively few data in the literature giving the magnitude of this resistance. Rohrer (1) gives values for the respiratory tract as a whole and for its various subdivisions. His values are derived theoretically by application of physical laws for the flow of gas in tubes to measurements of respiratory tracts obtained from cadavers.

To evaluate the resistance experimentally one needs to know simultaneously the rate of flow of air in the respiratory tract and the pressure gradient that exists between the alveoli and the outside. Although the former value is rather easily obtained, the latter is not. The most direct method of obtaining the pressure in the alveoli would be to insert a cannula into an alveolus. This method has been applied to dogs by Vuilleumier (2), but is obviously not suited to humans.

Another approach is the measurement of the intrapleural pressure by the method of Neergaard and Wirz (3). The difference between the static and dynamic intrapleural pressures represents the alveolar pressure plus the pressure required to overcome the viscous resistance of the lung tissue. The latter factor cannot be readily evaluated and the work of Bayliss and Robertson (4) on cat lungs indicates that it is not a negligible quantity. Vuilleumier (2) estimates that it amounts to about 20 per cent of the alveolar pressure.

A more indirect method, but one which readily lends itself to human subjects, is one proposed by Neergaard and Wirz (3) and more recently elaborated by Vuilleumier (2). Neither of these authors gives any extensive data, however. It is the purpose of the present paper to call attention to this interesting method and to present some data obtained from its application. The principle is as follows: The subject breathes in and out through a pneumotachograph which records the volume rate of flow on moving paper by way of a differential optical manometer. Another manometer records the pressure at the mouth piece. If the distal end of the system be suddenly occluded at any time during the breathing cycle, the flow drops to zero and the pressure in the whole system becomes equalized, resulting in a sudden rise or fall or pressure at the mouth, depending on whether the interruption occurred during inspiration or expiration.

This sudden change of pressure at the mouth is taken to be a measure of the

pressure gradient from alveoli to mouth that existed at the moment of interruption. The justification for this is as follows: The system at any given moment of the respiratory cycle can be regarded as being made up of numerous volumes of air each at its own pressure. When the flow is occluded and the pressure equalized, the equalized pressure multiplied by the total volume is the sum of all the initial pressure-volume products. If the volume of the alveoli is large compared to the other volumes (dead space of subject and apparatus), then the equalized pressure is essentially equal to the pressure that existed in the alveoli at the moment of interruption.

EXPERIMENTAL

The tachograph[3] used in the experiments employs a sintered metal (Porex) disc three inches in diameter as a resistance. The pressure drop across this had a linear variation with rate of flow of about $\frac{0.3 \text{ cm } H_2O}{100 \text{ cc/sec.}}$. The differential pressure of the tachograph and the pressure at the mouth were in most experiments measured by use of rubber membrane optical manometers, but in later experiments a Statham strain gage pressure transmitter feeding into a string galvanometer was used for one or both pressures.

Two types of interrupting devices were used. One was a metal stopcock placed in the system distal to the pneumotachograph. The handle of the cock was equipped with crank so that it could be turned easily by hand at a rate of two or three rotations a second. The bore of the cock was so constructed that the cock was open about one third of the time and closed about two thirds of the time.

Another apparatus for producing sudden interruptions was a stiff flat spring (made from a 100/sec. tuning fork) with one end securely fixed and with a rubber stopper larger in diameter than the distal end of the tachograph attached near the free end. The free end of the spring was held poised by the rim of a brass wheel so that the stopper was normally well away from the opening of the tachograph and offered no resistance to air flow. A notch was cut in the rim of the wheel at one point so that when the wheel was rotated the spring was suddenly released and the tachograph occluded once each revolution. The time required for interruption was less than 0.01 seconds. The duration of the interruption was one fifth of the time for a complete revolution of the wheel. The shaft of the wheel was equipped with a crank so that it could be turned manually at any desired speed.

Determination of relationship between rate of air flow and alveolar pressure. The subject sat connected to the apparatus by a rubber mouth piece and with the interrupter wide open. After a brief period to allow the subject to become

[3] This instrument was built according to the model described in Memorandum Report Serial No. TSEAA-696-107A from the Air Materiel Command, Wright Field, prepared by Wayland E Hull, April 28, 1947.

We wish to thank Dr. W. O. Fenn for originally suggesting this problem to us and for his advice during the course of the investigation.

accustomed to the apparatus, the valve was operated so as to interrupt the flow several times during each breathing cycle and a record covering several cycles was taken. The subject was then requested to breathe at rates of flow somewhat higher than normal and another record was taken. A sample of the sort of record obtained is shown in figure 1.

This record shows that at each interruption the rate of flow suddenly drops (or rises) to zero, where it remains during the period of interruption. At the same time the pressure at the mouth abruptly increases (or decreases) and then performs a series of damped oscillations around a slowly rising (or falling) line. The height above the line of zero pressure at which a line drawn through the centers of oscillations intersects the initial abrupt rise in pressure is taken as representing the pressure in the lungs at the moment of interruption. The

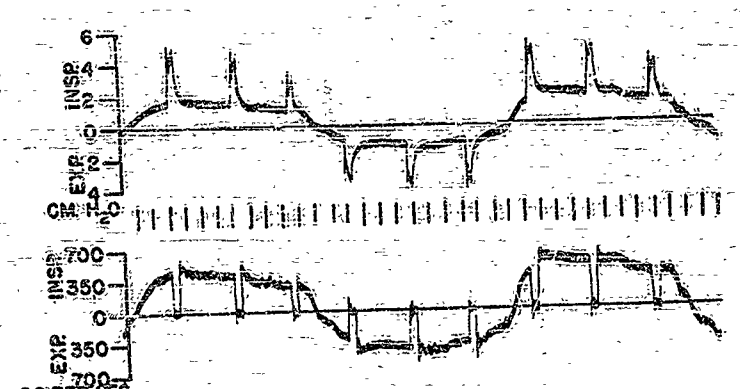


FIG. 1. TRACING OF SIMULTANEOUS RECORDS OF PRESSURE at the mouth (*upper curve*) and rate of flow (*lower curve*). Time intervals are 0.2 seconds. Records obtained by use of strain gage pressure transmitter.

pressure gradient between mouth and alveoli is obtained by subtracting the pressure in the mouth at the onset of interruption. The initial overshoot and subsequent damped oscillations are believed to represent the conversion of kinetic energy to pressure energy and its subsequent dissipation as pressure waves, which are reflected back and forth in the airways (a sort of 'water hammer' effect). The fact that the center of oscillation of these waves continues to rise (or fall) indicates that the chest continues to move during the period of interruption.

None of the subjects reported any unpleasant sensations while interruptions were being performed. Comparison of records taken with and without interruption indicate no marked disturbance in the normal breathing pattern.

Measurements of the records yielded data relating alveolar-mouth pressure gradients to rate of flow. The relationship obtained for one subject is shown in figures 2 and 3. In all, 21 subjects were examined in this fashion and the data for each subject were similarly plotted. A curve was drawn freehand through each set of data, and in figure 4 the curves for all individuals are shown.

Although a definite relationship appears to exist between alveolar pressures measured by this method and the simultaneously measured rates of flow, one may ask whether this method really measures the alveolar pressure. With this question in mind a model experiment was performed. A balloon was placed in a Drinker respirator and connected in series with a resistance of gauze sponge to the apparatus through a pipe in the respirator wall. A small tube leading from the inside of the balloon was connected to an optical manometer. In this

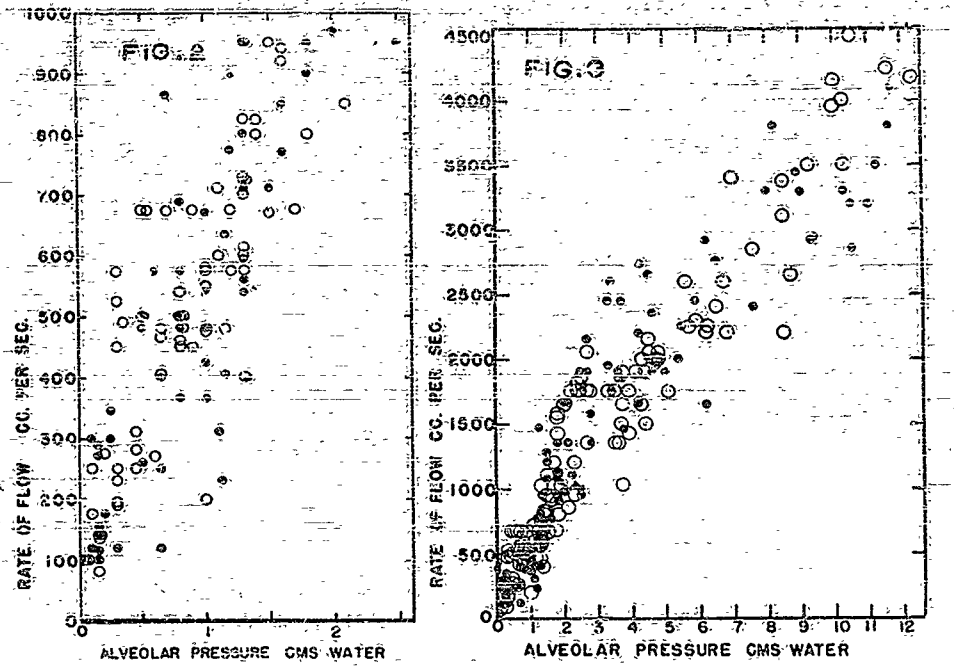


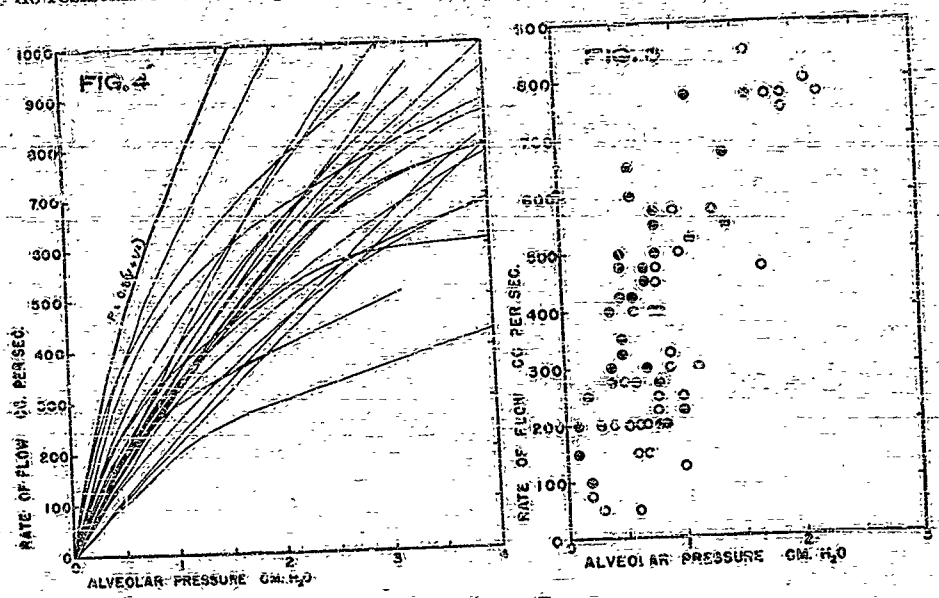
FIG. 2. RELATIONSHIP BETWEEN RATE OF FLOW AND ALVEOLI-MOUTH PRESSURE GRADIENT obtained for one subject. *Open circles* represent values obtained during inspiration, *solid circles*, during expiration.

FIG. 3. RELATIONSHIP BETWEEN RATE OF FLOW AND ALVEOLI-MOUTH PRESSURE GRADIENT for one subject. This figure includes the data shown in figure 2 but is extended to show higher rates of flow.

fashion the pressure within the balloon could be recorded directly. The respirator was sealed and the pump turned on so as to artificially ventilate the balloon. The 'alveolar' pressure of the balloon by the method of interruptions and by the direct method was recorded on the same film. Records of the sort shown in figure 5 indicate good agreement between the two methods. Admittedly the model is not a perfect imitation of the human lung, but it seems sufficiently similar in principle to give one confidence in the values obtained by the method of interruptions. Vuilleumier (2) also describes model experiments which indicate the validity of the method of interruptions.

DISCUSSION

The data have been plotted with rate of flow as a function of alveolar pressure. The resistance of the respiratory tract to air flow is represented by the reciprocal



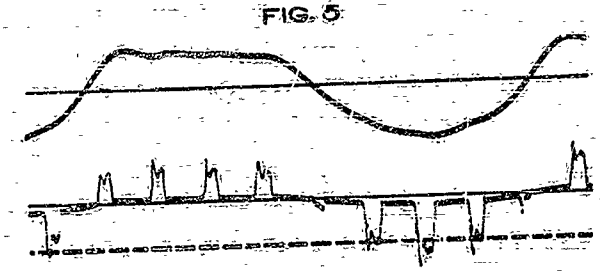


FIG. 4. RELATIONSHIP BETWEEN RATE OF FLOW AND ALVEOLI-MOUTH PRESSURE GRADIENT for 21 subjects. Rohrer's theoretical curve is shown for comparison. Since most of the subjects did not exceed a velocity of 1000 cc. per second, no higher values are shown.

FIG. 5. SIMULTANEOUS RECORDS OF PRESSURE in a balloon as measured directly (*upper curve*) and by the method of interruptions (*lower curve*). Time intervals shown at bottom are 0.2 seconds.

FIG. 6. RELATION OF RATE OF FLOW to alveolar pressure at two different lung volumes. *Solid circles* represent subject breathing with lungs as empty as possible; *open circles*, subject breathing with lungs as full as possible.

slope of the curve fitting these points. According to the theoretical reasoning of Rohrer (1), the pressure drop along the respiratory tract is due to:

1. Viscous resistance with the pressure drop varying linearly with rate of flow.
2. Resistance due to changes in direction of flow (as in branching) and changes in x-sectional area of the airway with the pressure drop proportional to the

square of the rate of flow. This type of resistance is almost entirely confined to the upper airways (larynx and distal structures).

3. Resistance due to turbulence with the pressure drop varying with approximately the square of the rate of flow.

From measurements on cadavers Rohrer concluded that the critical velocity for transformation from streamline to turbulent flow would not be attained until the flow exceeded five liters per second, a rate that is seldom reached except in coughing. For any ordinary breathing, therefore, only the first two of the above factors would contribute to the pressure drop, and the equation relating pressure to rate of flow should have the form $P = K_1 V + K_2 V^2$.

The value of each of these constants, as determined by Rohrer from anatomical measurements, is about 0.8, so that the equation becomes $P = 0.8 (V + V^2)$, when P is expressed in centimeters of water and V in liters per second.

The curve for this equation has been plotted in figure 4 for comparison. All individuals show a higher resistance than the equation predicts, but it appears that an equation of this form would fit most of the data reasonably well, although the constants would have to be adjusted for each individual as would be expected.

The mean pressure for a flow of 250 cc/sec. is 0.7 cm. H_2O (range of 0.3 to 1.4 cm. H_2O), and for a flow of 500 cc/sec. is 1.8 cm. H_2O (range of 0.8 to 5.0 cm. H_2O). These figures agree well with values measured from the sample curves published by Vuilleumier. Values obtained by Neergaard and Wirz, using this method on three normal individuals, are about twice as great, but, judging from the form of the recordings shown by these authors, their method of interrupting was not sufficiently abrupt.

The scatter of the data for each individual (typically shown in figures 2 and 3) is probably due not only to experimental error in the measurement of the rates of flow and pressures but also to real physiological variations, especially at the high rates of flow. Slight changes in the configuration of the glottis and in the position of the tongue and other structures of the throat could appreciably alter the alveolar pressure required for a given rate of flow.

The results do not indicate any consistent difference between the resistance during inspiration and that during expiration. This is contrary to the observations of Neergaard and Wirz (3), who found that on three subjects expiratory resistance was greater than inspiratory. However, they were using the method of intrapleural pressure measurement and their values include the viscous resistance of the lung tissue. Moreover, their subjects were not normal, two of them having bronchial asthma and one tuberculosis.

Certain sources of error in the method must be mentioned in appraising the results of the present study. As stated above, the justification for equating the equalized pressure following interruption to the alveolar pressure is that the dead space volume is negligible as compared to the alveolar volume. Actually our apparatus has a dead space of about 650 cc. This would make the measured alveolar pressures lower than the actual by about 15 to 20 per cent, depending on the alveolar volume which, of course, varies from one individual to another.

The effect of voluntarily varying the alveolar volume has been tested on one individual by having him breathe with his lungs as full of air as possible and then with his lungs as empty as possible. The results are shown in figure 6 and indicate that the highest apparent alveolar pressure for a given rate of flow occurs when the lungs are most inflated, the lowest when the lung volume is low. Presumably these apparent differences in alveolar pressure are due in part at least to the difference in the size of the alveolar volume in relation to the dead space in the two conditions. This effect could be minimized by use of an apparatus with a small dead space.

Another factor, however, would tend to make the measured values somewhat too high and would compensate for the error just discussed. After the moment of complete occlusion a finite time (estimated by Vuilleumier to be in the order of 1/200 sec.) is required for the pressure in the system to become equalized. During this time the chest continues to move, thus raising the pressure above that which existed at the moment of interruption. The magnitude of this error will depend largely on the rate at which the chest is moving at the moment of interruption.

In spite of the sources of error mentioned above, this method for the estimation of alveolar pressures should, because of its relative simplicity and painlessness, prove useful in the investigation of both clinical and physiological problems in the mechanics of respiration.

SUMMARY

1. Measurements of alveolar pressure and simultaneous rate of flow of respired air of 21 human subjects are presented.

2. The data for each subject can be described by an equation of the form $P = K_1V + K_2V^2$, where P is the alveolar pressure and V is the volume rate of flow. The constants K_1 and K_2 differ for different individuals.

3. In the average subject an alveolar pressure of 1.8 cm H_2O is required to produce a flow of 500 cc. per second.

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Effect of Gas Density on Resistance to Respiratory Gas Flow in Man

ARTHUR B. OTIS AND WELDON C. BEMBOWER.

RELIEF OF CERTAIN TYPES of dyspnea by substituting a mixture of helium and oxygen for air as the respired gas has been demonstrated by Barach (1, 2) and others (3–5). The beneficial effect is attributed to the fact that a smaller pressure gradient is required to move the less dense gas through a resistance (2). Dean and Visscher (6) by experiments on dog lungs have confirmed the belief that the apparent reduction in resistance to gas flow is related to the lesser density of the helium-oxygen mixture, and have further shown that it is actually due to a decreased turbulence. The relative ease of breathing which is subjectively noted at reduced barometric pressures (e.g. in a high altitude chamber) is presumably a similar phenomenon.

The purpose of this paper is to present data showing the magnitude of the reduction in resistance to flow that occurs in the human respiratory tract when the gas density is decreased by substituting helium-oxygen for air or by decreasing the barometric pressure, and to demonstrate that the observed decrease in resistance is adequately explained on the assumption that it is due to a decreased turbulence.

THEORETICAL

The pressure gradient required to move air in and out of the lungs is dependent on the geometry of the respiratory tract and on the density and viscosity of the respired gas. According to Rohrer (7) the relationship for the human respiratory tract between the volume-rate of flow and pressure gradient is $P = K_1V + K_2V^2$ where P is the pressure gradient and V the rate of flow. The validity of an equation of this form has been to some extent confirmed experimentally by Otis and Proctor (8). The linear part of the equation represents the stream-line flow component and its constant, K_1, includes the viscosity of the respired gas. The quadratic part represents the local turbulence occurring where the airways branch or suddenly change diameter, and its constant, K_2, includes the density of the air.

Reduced barometric pressure or substitution of an 80 per cent helium–20 per cent oxygen mixture for air diminishes the density of the respired gas but alters the viscosity only slightly and should change the constant K_2 without greatly affecting K_1. (Both constants are dependent in part on the dimensions and configuration of the respiratory tract, but it seems reasonable to assume that these factors would be independent of the density of the gas breathed.)

EXPERIMENTAL

The alveolar pressure gradient and rate of flow were measured by the method previously described by Otis and Proctor (8) but with a somewhat more refined apparatus. The flow meter utilized 400-mesh monel gauze as a resistance. It had a dead space of only 70 cc., a resistance of 1 mm. H_2O/200 cc/sec., and gave linear calibration up to at least 4500 cc. per second. The interrupter was constructed in the form of a slide valve. It was closed by a solenoid magnet and returned to the open position by a counter-spring. Recording of the alveolar pressure and of the differential pressure from the flow meter was accomplished by means of strain gage pressure transmitters (Statham Laboratories) connected with a carrier wave amplifier which fed into the galvanometers of an oscillograph (Hathaway Instrument Co.).

For measurements of the effect of substituting helium-oxygen mixtures for air, the distal end of the flow-meter was connected to a set of inspiratory-expiratory valves. During the air-breathing period both valves were left open to the air on the side away from the subject. For the He-O_2 breathing period the inspiratory valve was switched to a spirometer containing 80 per cent helium–20 per cent oxygen. The general procedure was to record for about a minute with the subject breathing air, then to have the subject take several deep breaths of the He-O_2 mixture in order to flush the air out of the lungs, and finally to take a record with the subject breathing the mixture. During the periods of recording the subject was requested to breathe normally at first, then to increase his ventilation somewhat so as to obtain higher rates of flow.

In order to determine the effect of reduced barometric pressure, subjects were taken to the desired altitude in our low pressure chamber. Except during the actual measurements the subjects breathed oxygen from a demand system. When measurements were desired, the subject took a deep breath of oxygen, put on a nose clip, and then breathed from the mouth piece of the alveolar pressure apparatus. The distal end of the flow meter was, in these altitude experiments, connected to a 50-liter Douglas bag containing oxygen. Since only about a minute was required to obtain a set of measurements, the re-breathing that occurred with this arrangement was not excessive.

RESULTS

Comparison of Air and 80 Per Cent He–20 Per Cent O_2. The data obtained from measurements of the records taken on one individual are indicated by the points plotted in figure 1. Since our method shows no consistent difference between inspiratory and expiratory resistance to flow (8), no distinction has been made between points obtained during inspiration and those obtained during expiration. From inspection of the plotted points it is obvious that in general for a given rate of flow a smaller pressure gradient is required when helium–oxygen instead of air is the respired gas.

According to the theoretical discussion above, it should be possible to fit each of the two sets of data with a curve of the form given by *equation 1* in which K_1 should be approximately the same for both curves, but K_2 for air

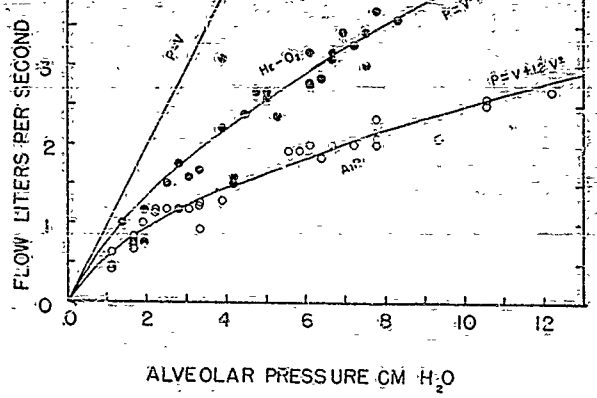

Fig. 1. Relationship between rate of flow and alveoli-mouth pressure gradient obtained for one subject, breathing air (open circles) and 80% He–20% O_2 (solid circles).

breathing should be about three times that for the helium-oxygen mixture, since the ratio of the density of air to that of a mixture of 80 per cent helium–20 per cent oxygen is approximately 3:1. Such a pair of curves have been constructed on figure 1, which seem to give a good fit to the experimental points. In addition, the straight line, $P = K_1V$, which represents the viscous flow component common to both gas mixtures, has been drawn. The distance along the abscissa from a chosen rate of flow on the axis of ordinates to this line represents the pressure required to overcome the viscous resistance for that rate of flow for either air or helium–oxygen. The additional distance that must be traversed along the same abscissa until the curve for $He–O_2$ is intercepted represents the additional pressure that must be developed to overcome the turbulence breathing this gas mixture. The pressure required to overcome turbulence for air breathing can be represented in a similar fashion.

Comparisons between air and 80 per cent helium–20 per cent oxygen as

the inspired gases were made on 20 individuals. In each case the data were graphed as in figure 1 and a free-hand curve was drawn through each set of plotted data. In each case the curve for the helium–oxygen lay above that for air. The points plotted in figure 2 are the means of the alveolar pressure values read off the individual curves of the 20 subjects at each of several rates of flow. These points have been fitted with curves of the form given by *equation* 1 and in accordance with the theory discussed above. Although the fit of the curves to the points is not perfect, it is adequate as judged by the fact that the lines showing the extent of the standard error of the means which the points represent are intersected in all but one instance. It should be pointed out, however, the the deviation of the theoretical curves from the experimental

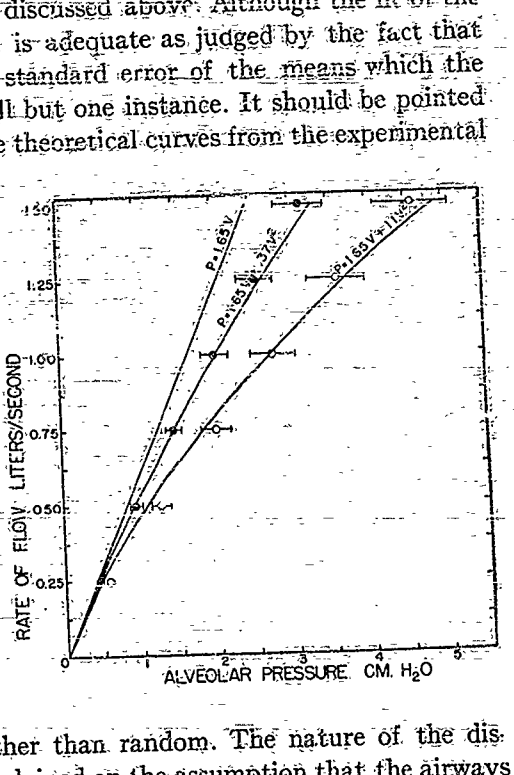

Fig. 2. Relationship between rate of flow and alveoli-mouth pressure gradient obtained for 20 subjects, breathing air (open circles) and breathing 80% He–20% O_2 (solid circles). Each point indicates the mean alveolar pressure of all subjects for a particular rate of flow. The horizontal lines through the points show the magnitude of the standard error of each mean.

points seems to be systematic rather than random. The nature of the discrepancy is such that it could be explained on the assumption that the airways offer relatively less resistance at the higher rates of flow. It may be that there is a mechanism whereby some parts of the respiratory tract become more dilated as the flow rate (or the pressure) increases. The glottis, for example, is capable of considerable variation in its aperture, and it is known to change rhythmically with the breathing cycle.

Comparison of Different Barometric Pressures. Measurements were made on 3 subjects at ground level and at the simulated altitudes of 18,000 and 36,000 feet. Figure 3 shows the results obtained at ground level and at 36,000 feet on one subject (the same subject is represented in fig. 1). The curves drawn on this graph were fitted according to the theory that the value for K_2 at 36,000 feet should be a little less than one-fourth that at ground level (ratio of the relative densities at the two altitudes).

The data from each of the 3 subjects at each of the three barometric pressures were grouped into class intervals according to velocity of flow, each

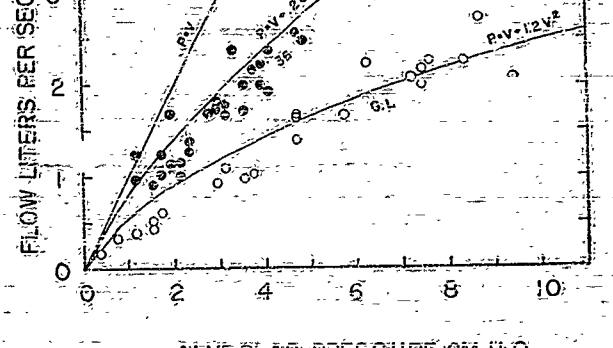

Fig. 3. RELATIONSHIP BETWEEN RATE OF FLOW and alveoli-mouth pressure gradient obtained for the same subject represented in figure 1, breathing O_2 at ground level (open circles) and at 30,000 feet (solid circles).

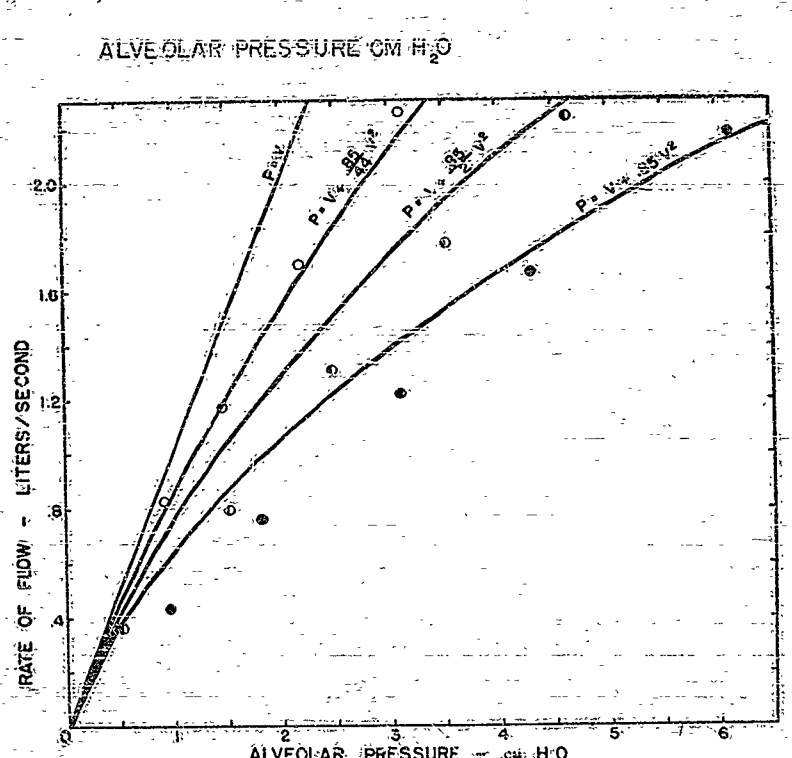

Fig. 4. RELATIONSHIP BETWEEN RATE OF FLOW and alveoli-mouth pressure gradient obtained for 3 individuals breathing oxygen at ground level (closed circles), and at 18,000 feet (half-open circles) and at 36,000 feet (open circles).

interval having a range of 500 cc/sec., and the mean alveolar pressure and mean velocity of flow were calculated for the values falling into each class in-

terval. The means from similar class intervals for the three subjects were averaged and the resulting grand means were plotted in figure 4. The curves in this figure were drawn according to the theory described above and seem to give an approximate fit, but show a deviation similar to that observed in the comparison between helium–oxygen and air.

COMMENT

It would be interesting to make similar measurements at pressures greater than atmospheric, but facilities for these were not readily available to us. However, by extrapolating the present data one can perhaps get a reasonable estimate of the alveolar pressures required under such conditions. For example, our average subject (fig. 2) developed an alveolar pressure of 2.75 cm. H_2O in moving air at 1 liter/second at ground level. At an environmental pressure of 4 atmospheres, as in diving, calculation shows that 6.05 cm. H_2O would be required for this rate of flow $(1.65 + (4 \times 1.1))$. Breathing at 2 liters/sec. would require 7.7 cm. H_2O at ground level, but 20.9 cm. H_2O at 4 atmospheres $(2 \times 1.65 + 4 \times 1.1 \times 2^2)$.

Dr. Kenneth Donald (personal communication) states that at a pressure of 8 atmospheres the turbulence is so great that one can actually feel eddy currents in the air as it flows through the mouth. At this barometric pressure the gradient required to respire at a rate of 2 liters/second would be 38.5 cm. H_2O according to our extrapolation. On the other hand, breathing at this velocity at an altitude of 46,000 feet would require only about 4 cm. H_2O.

In making the theoretical calculations in this paper we have assumed that helium–oxygen has the same viscosity as air (actually the viscosity of helium is about 10 per cent greater than that of nitrogen). The effect of carbon dioxide and water vapor on the viscosity and density of the respired gas has also been neglected. We feel that the error in these approximations is less than that in the actual measurements of the alveolar pressures and rates of flow.

SUMMARY

The alveolar pressures required to produce various velocities of respiratory gas flow have been measured in 20 human subjects breathing 1) air and 2) 80 per cent helium–20 per cent oxygen. In 3 subjects a similar comparison has been made between air breathing at ground level and at simulated altitudes of 18,000 and 36,000 feet. Less alveolar pressure is required to produce a given velocity of flow when a person breathes 80 per cent helium–20 per cent oxygen at ground level or air at altitude than when he breathes air at ground level. Theoretical treatment of the data indicates that this effect is due to a decreased turbulence in the less dense gases. The data also suggest that some parts of the respiratory tract may dilate when one breathes at high velocities.

We thank Dr. Wallace O. Fenn and Dr. Hermann Rahn for helpful suggestions and for participation in some of the experiments and Miss Helen Jacobs for technical assistance.

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Effect of Adrenaline on Resistance to Gas Flow in the Respiratory Tract and on the Vital Capacity of Normal and Asthmatic Subjects

MURRAY B. SHELDON, JR. AND ARTHUR B. OTIS.

THE MEASUREMENT OF THE VITAL CAPACITY is frequently used in clinical investigation as an index of changes in the degree of bronchiolar constriction following administration of various drugs (1–7). Plotz (5) and Curry (1) have recognized, however, that changes in vital capacity do not, at least on *a priori* basis, necessarily imply a change in bronchiolar diameter.

In the present study of six normal and six asthmatic subjects a technique described by Vuilleumier (8) and more recently employed in this laboratory (9–11) has been utilized. This method seems to give a measure of the resistance of the respiratory tract to gas flow, and it was felt that such measurements might serve as a better index to changes in bronchiolar diameter than does vital capacity. Consequently, parallel measurements of alveolar pressure by this method and of vital capacity have been made before and at various intervals after subcutaneous injection of adrenaline hydrochloride in an attempt to determine changes in resistance of the respiratory tract to gas flow and to test to some extent the validity of using vital capacity measurements as an index to bronchiolar tone.

METHODS

The pressure gradient between alveoli and mouth was measured by the method of sudden interruptions (8, 9). The apparatus used was that described by Otis and Bembower (10). A sample of the type of recording obtained by

this technique is shown in figure 1. In the present experiments, each trial was approximately 30 seconds in duration and involved from 20 to 35 interruptions.

Vital capacities were measured by having the subject exhale maximally into a spirometer following a maximal inhalation. Each value reported below is the average of from 4 to 6 trials and is expressed at body temperature and pressure, saturated.

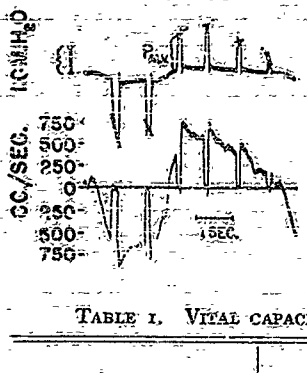

Fig. 1. Simultaneous recording of pressure at the mouth of the subject (*upper record*) and pneumotachogram during one complete respiratory cycle (*lower record*). The method of estimating alveolar pressure from the change that occurs during interruption is indicated.

Table 1. Vital capacity measurements on normal and asthmatic subjects

Subject	Before	Time in minutes after adrenaline administration					
		5	15	30	60	90	120
N1					5.39	5.35	5.42
N2	4.85	4.84	4.84	4.85	4.86	4.89	4.89
N3	5.14	5.10	5.21	5.05	5.10	5.11	5.15
N4	5.82	5.85	5.70	5.81	5.72	5.85	5.75
N5	3.64	3.58	3.62	3.56	3.62	3.63	3.63
N6	3.49	3.45	3.26	3.42	3.39	3.46	3.43
A1	1.27	1.93	1.85	1.62	1.27	0.93	1.02
A3	5.58	5.75	5.78	5.75	5.78	5.80	5.68
A4	6.28	6.56	6.57	6.65	6.64	6.64	6.61
A5	2.07	2.26	2.53	2.62	2.62	2.56	2.66
A6	2.47	2.59	2.57	2.84	2.65	2.57	2.46
A7	1.99	2.35	2.42	2.52	2.66	2.86	2.88

Volumes in liters (B.T.P.S.).
N: normal; *A:* asthmatic.

Procedure

Six normal and 6 asthmatic subjects were studied. Three of the asthmatics had been asymptomatic for several weeks and the others were using adrenaline currently. None of the subjects was tested during an attack, and each subject was instructed to refrain from smoking or using adrenaline for a period of at least 2 hours preceding the tests.

The general procedure was as follows. Vital capacity measurements were made with the subject standing. Then, seated and with a nose clip applied, the subject breathed through a mouthpiece connected to the alveolar pressure

apparatus while a recording was made. Following these measurements, a subcutaneous injection of from 0.35 to 0.5 cc. adrenaline hydrochloride 1/1000 was made. Measurements of vital capacity and alveolar pressures were begun 5, 15, 30, 60, 90 and 120 minutes subsequent to the injections.

Results

Vital capacity measurements are shown in table 1. The alveolar pressures obtained in each trial were plotted against the corresponding velocities of flow. Since no consistent difference between inspiratory and expiratory resistance to flow was demonstrable, points obtained in both phases of the breathing

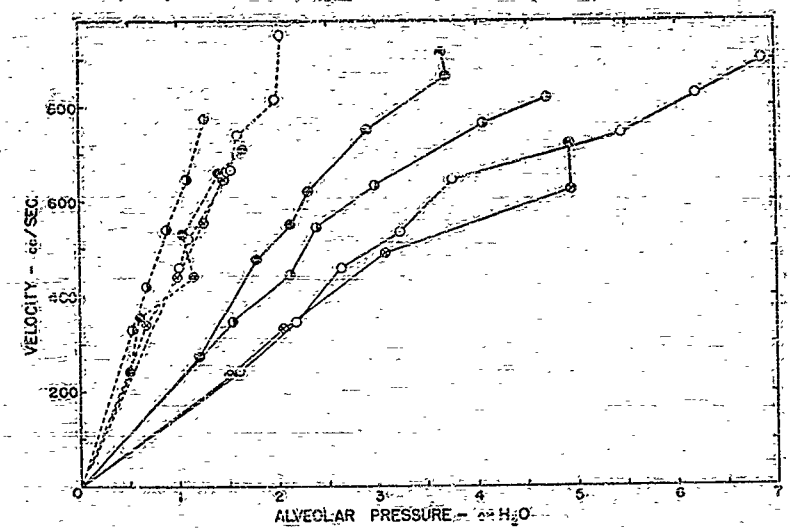

Fig. 2. Alveolar pressures at different velocities of flow before and at intervals after the administration of adrenaline. *Solid lines* indicate asthmatic subject (*A1*) and *dotted lines* indicate normal subject (*N4*). *Symbols* indicate pressure-velocity relationships at the following periods: *open circles* before adrenaline, *closed circles* 5 minutes after adrenaline, *half closed circles* 1 hour after adrenaline and *x'd circles* 2 hours after adrenaline. Curves for 15, 30 and 90 minutes after administration of adrenaline have been omitted from the figure for the purpose of clarity.

cycle were plotted together. A mean was calculated for all points falling in each 100 cc/second range of velocity of flow and the resulting average points were used as a basis for drawing curves such as those shown in figure 2, in which results of measurements on a normal and on an asthmatic subject are shown.

The data were further summarized by reading from each of the curves, such as those shown in figure 2, the alveolar pressure at a velocity of flow of 500 cc/second. These values, which are a measure of the resistance to gas flow through the respiratory tract, were then plotted along with the vital capacity measurements against time as shown in figures 3 and 4.

In the normal group, no significant changes in vital capacity occurred, although 3 of the 6 subjects showed a moderate decrease in resistance to flow following adrenaline.

All asthmatic subjects showed an increased vital capacity following the administration of adrenaline. This increase, which was detectable 5 minutes after the injection, was in most subjects well maintained or even enhanced during the following 2 hours (fig. 3). In *subjects A1* and *A5*, however, the vital capacity first rose and then later fell back to the initial value or even below.

In general, the resistance of the respiratory tract to gas flow showed a change inverse to that of vital capacity; that is, the resistance fell as the vital capacity increased. In *A6*, however, the resistance increased during the period of observation even while the vital capacity was rising and in *A5* the resistance remained nearly constant, although a considerable increase in vital capacity was observed.

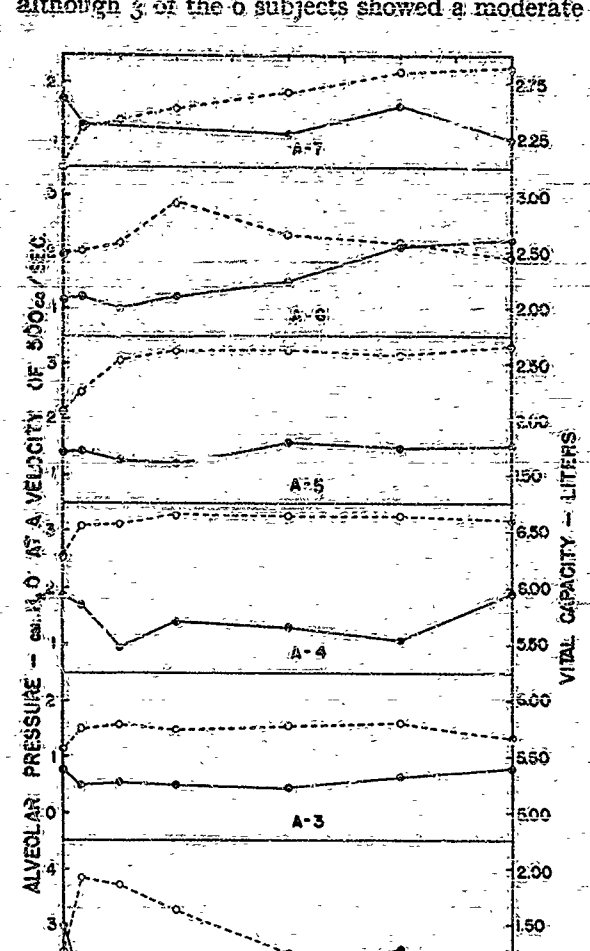

Fig. 3. ALVEOLAR PRESSURES AT A VELOCITY of 500 cc/second flow (*solid lines*) and simultaneous vital capacity measurements (*dotted lines*) in 6 asthmatic subjects (*A1–A7*) before and at definite intervals after the administration of adrenaline.

It is of no particular value to consider in detail the case histories of the asthmatics used in this study further than to state that the most marked changes in alveolar pressure and vital capacity were seen in a 36-year-old housewife (*A7*, fig. 3) who had recovered from her most recent attack after taking one-half cc. of

adrenaline 2 hours prior to the present determination. Least significant changes were seen in (*A* 3, fig. 3) a 24-year-old medical student with seasonal summer asthma who had been asymptomatic for 10 months. The other asthmatic subjects, all between the ages of 27 and 72 years, had been asymptomatic at variable periods between these extremes. Age, infectious and intrinsic factors, duration of asthma, and sex did not appear to be related to the type of response seen.

The observation that an increase in vital capacity following adrenaline is not always accompanied by a decrease in resistance to flow suggests that two distinct actions of adrenaline may be involved: *1*) Relaxation of the bronchiolar musculature; and *2*) constriction of pulmonary blood vessels.

The first of these would, by enlarging the diameter of the bronchioles, be expected to decrease the resistance to gas flow, and also to some extent perhaps to increase the vital capacity. The second mechanism, by decreasing the amount of blood in the thorax, would allow more room for air. If, as seems

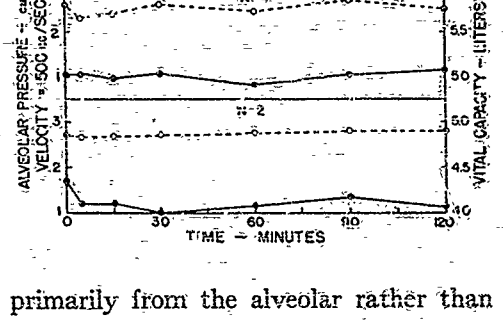

Fig. 4. ALVEOLAR PRESSURES AT A VELOCITY of 500 cc/second flow (*solid lines*) and simultaneous vital capacity measurements (*dotted lines*) in 2 normal subjects (*N2* and *N4*) before and at definite intervals after the administration of adrenaline.

possible, the displaced blood came primarily from the alveolar rather than from the bronchiolar walls, the vital capacity would be increased while the resistance to gas flow would not be changed.

The direction and degree of changes in vital capacity and in resistance to flow in a given individual following adrenaline administration would depend, therefore, upon the sum of the actions of these two independent mechanisms.

It is suggested that further observations of the sort recorded above be undertaken in the evaluation of the effects of other therapeutic and toxic agents on the bronchial tree. It is possible, for example, that the effects of histamine in reducing the vital capacity of active asthmatics (Curry 1, 2) may be due to pulmonary vasodilation rather than broncho-constriction. Investigation along these lines is warranted in an effort more clearly to establish whether bronchial asthma may fall into groups largely dependent on either bronchial spasm, pulmonary vascular dilation or a combination of these and to determine whether certain drugs are more efficacious against one or the other mechanism.

Summary and Conclusions

Measurements of resistance to air flow and of vital capacities have been made in normal and asthmatic subjects before and at definite intervals after administration of adrenaline. Although all asthmatics had increased vital capacities after adrenaline, alveolar pressures were lower, higher or unchanged which indicates the likelihood that adrenaline produces pulmonary vascular constriction rather than bronchiolar dilation in certain cases. Further investigation is warranted to establish more exactly the relative importance of the bronchiolar and vascular components of asthma and to evaluate more precisely the mode of action of certain sympathomimetic drugs and toxic agents.

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Some Physiological Effects Resulting from Added Resistance to Respiration

By Major Clarence C. Cain, USAF, and Arthur B. Otis

THIS INVESTIGATION is concerned with the physiological effects of added resistance to breathing and will be described under the following headings: (1) effects of added resistance on respiratory patterns, ventilation, and gas exchange; (2) work and efficiency of breathing on added resistance; (3) effect of resistance on the ballistocardiogram.

Air flow characteristics may be of two general types: (1) turbulent flow, in which the rate of flow varies as the square root of the pressure head, and (2) laminar or streamline flow, in which the rate of flow varies directly with the pressure head. The type of resistance used in this investigation permitted streamline flow.

Effect of Added Resistance on Respiratory Patterns, Ventilation and Gas Exchange

The apparatus used in this phase of the investigation recorded the rate of flow and mouth pressure simultaneously on photographic paper (Fig. 1). The flowmeter was fitted on one side with a mouthpiece, and the other side was attached by a Y-tube to two parallel tubes. The resistance disk was fitted in one arm of the Y and a stopcock in the other. By closing the stopcock the air flow was directed through the resistance disk. A mouthpiece was used in preference to a mask to minimize the possibility of air leaks and to reduce the dead space.

Pressure Recording.—A small tube at right angles to the breathing circuit near the mouthpiece was connected to a strain gage (Statham pressure transmitter). Changes occuring during inspiration and expiration were transmitted to the strain gage, which was connected to a string galvanometer so that pressure changes were reflected in the deflection of the galvanometer.

Rate of Flow Recording.—The flow meter consisted of a porous bronze disk, 3 inches in diameter and ½-inch thick, sealed air tight between two flanges.* The porous nature of the disk permitted streamline flow, and the pressure gradient developed across the disk was transmitted to a second strain gage and string galvanometer.

Resistance and Deadspace.—Two porous bronze disks, 1 inch in diameter and 1/16-inch thick, were used for the resistance. These disks were pro-

*This instrument was built according to the model described in Memorandum Report, Serial No. TSEA-696-107A from the Air Materiel Command, Wright Field, prepared by Wayland E. Hull, April 28, 1947.

duced by the manufacturer (Moraine Products, Division of General Motors Corporation) by bonding together carefully graded spheres of metal, resulting in a controlled porosity. The lower resistance disk (R-1) offered a resistance to air flow of 0.067 mm. H_2O/c.c./sec., and the higher resistance disk (R-2) with smaller size passages offered a resistance of 0.308 mm. H_2O/c.c./sec.

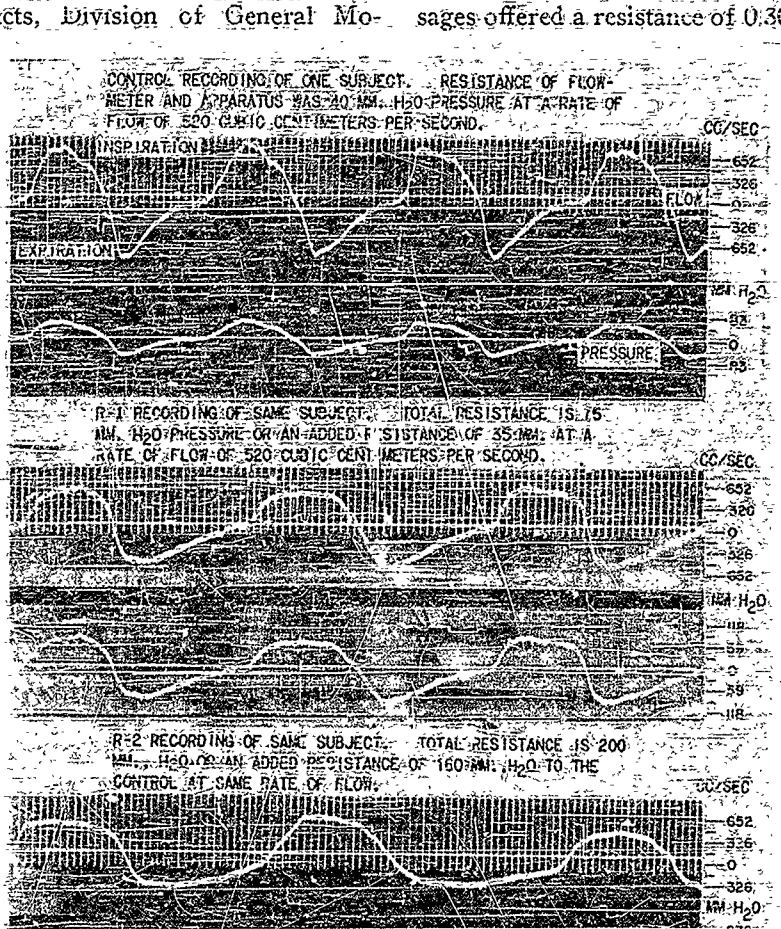

Fig. 1. Simultaneous flow and pressure recording of the same subject, control, R-1 and R-2. The upper curve of each record is the rate of flow; the lower is inspiratory and expiratory pressure. The curve above zero line represents inspiration and below is expiration. Time is indicated in 1/5 seconds. Note zero line is slightly below reference line of the flow curve.

The flowmeter and apparatus itself offered a resistance to air flow of 0.077 mm.H_2O/c.c./sec. All control records were taken with this amount of resistance present, and in the experi-

TABLE I. EFFECTS OF RESISTANCE ON RESPIRATORY PATTERNS

	Total Time in Sec.	Time to Reach Maximum Rate of Flow in Sec.	Maximum Pressure mm. H_2O	Maximum Rate of Flow c.c./sec.	Tidal Volume c.c.	Mean Rate of Flow c.c./sec.	Max. RF / Mean RF
Inspiration							
Control	2.31	.82	43	710	1070	462	1.54
R-1	2.37	.79	86	653	1075	454	1.44
R-2	2.71	.74	214	526	1024	378	1.39
Expiration							
Control	3.13	1.16	42	692	1070	342	1.91
R-1	3.32	.80	63	514	1075	324	1.64
R-2	4.18	.97	135	384	1024	245	1.57

These data are the averages taken from 120 inspirations and expirations of five subjects. RF is "rate of flow" and the last column is the ratio of the maximum rate of flow to the mean rate of flow. This ratio describes the approximate shape of the respiratory pattern in respect to the maximum height above the mean (Bretschger 1925). If this ratio should be one, it would necessarily mean that the pattern is rectangular in shape, with the width of the rectangle equal to the mean rate of flow. A ratio of two would indicate the maximum height of the pattern to be twice the mean and would in general suggest a triangular pattern.

mental procedures R-1 or R-2 was added to it. The measured dead space of the flowmeter and apparatus was 250 c.c.

Procedure.—By means of mirrors, the light beams from the two galvanometers (recording rate of flow and pressure) were directed on the slit of a recording camera. An electrical timer was placed so that it recorded on the edge of the record.

The subject was seated in position and rested until respiration was quiet and regular. The nose clip and mouthpiece were then adjusted, and the subject breathed through the flowmeter and apparatus for five minutes to adjust to the resistance and dead space, before taking the control record. The resistance was then added to the circuit, and after five minutes a resistance record was obtained, followed by a recovery record five minutes after switching the resistance out of the circuit. The same procedure was repeated for the second resistance, and each record taken consisted of at least four respirations each. Figure 1 is a typical record obtained and illustrates the change in pattern due to resistance.

Subjects.—Five healthy male subjects were used in this investigation. All were experienced subjects who had frequently participated in various types of respiratory experiments and, since the results were readily reproduced, were considered to be free from all psychological factors which would affect the experiment.

Results and Discussion.—A total of 120 inspirations and expirations from the five subjects were examined for the increased total time, time to reach maximum rate of flow, maximum pressures, maximum rates of flow, tidal volumes (obtained by integration of the flow curves with a planimeter) and mean rates of flow. The averages for all subjects are shown in Table I.

A mean respiratory cycle constructed from measurements made on records of four cycles for each individual is shown in Figure 2. Each respiratory phase was divided into five equal time intervals, and the values for rate of flow and for time were each averaged to obtain the data for the construction of the mean cycle.

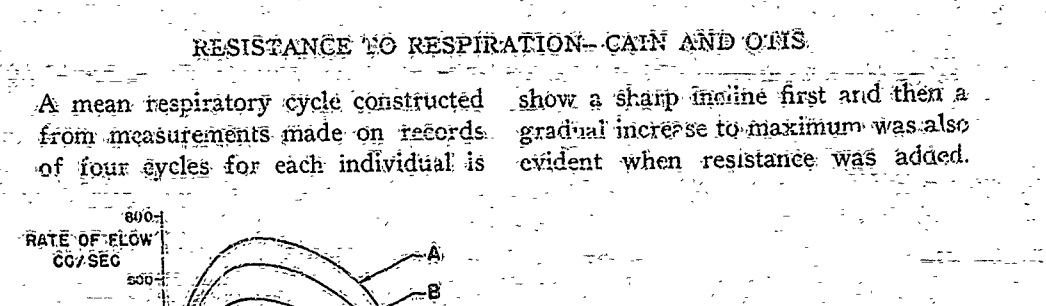

Fig. 2. One respiratory cycle constructed from the mean inspiratory and expiratory curves, showing the effect of resistance on a complete respiratory cycle. (A) Control with resistance of flowmeter and apparatus of 0.077 mm.H_2O/c.c./sec. (B) Resistance R-1, an added resistance of 0.067 mm.H_2O/c.c./sec. Resistance R-2, an added resistance of 0.308 mm.H_2O/c.c./sec.

The inspiratory flow pattern with minimum resistance showed in most cases a sharp and fairly uniform acceleration until a rate of flow of about 75 per cent of maximum was reached. The acceleration gradually decreased until maximum flow was obtained. The first inspiratory pattern in Figure 1 is fairly typical of this initial acceleration. The average time for all subjects to reach a maximum rate of flow on the control was .82 seconds, and decreased slightly when resistance was added. The general tendency for the slope of the inspiratory curve to show a sharp incline first and then a gradual increase to maximum was also evident when resistance was added. The flow was maintained within 10 per cent of maximum for approximately 50 per cent of the time of inspiration, and then showed a steady decline to zero flow. Silverman[10] noted that as the amount of resistance increased, the inspiratory curves tended to become smoother and less in amplitude. The same effect has been noted in this investigation.

The expiratory pattern shows a more marked change when the resistance is added. On the control the curve shows a steep slope until it reaches maximum rate of flow and immediately starts a slow decline to zero, approaching a triangular shape. As resistance is added, the amplitude decreases until the shape of the curve with R-2 approaches that of a sector of a circle, a gradual increase to maxi-

mum and then the same gentle slope back to zero. There seems to be an individual variation in the time required to reach maximum expiratory flow. Generally a decrease in time to reach maximum rate of flow was observed with R-1, followed by a slight increase with R-2 but still less than the control.

There was no evidence of a pause at the end of inspiration for any of the subjects. In the control condition with minimal resistance present, expiratory flow showed a pause of 0.2 to 0.9 seconds before inspiration began, on three of the five subjects. As resistance was added, this pause at the end of expiration disappeared, except in one of the five subjects while breathing with the light resistance, R-1, and was not evident with the heavy resistance, R-2, on any of the subjects.

Added resistance resulted in an increased time for inspiration and expiration, but the increase is much greater during expiration. From Table I it may be seen that R-1 increased the time of inspiration by 2.6 per cent.; R-2 increased it by 17 per cent. During expiration, R-1 showed an increase of 6 per cent, while R-2 gave 33.5 per cent increase. The effect of resistance on time of inspiration and expiration was investigated by Lippelt.[5] He recorded an increase in time of inspiration from a normal of 2.2 seconds to 3.9 seconds with resistance, and during expiration from a normal of 2.6 to 4.2 seconds due to resistance. It is difficult to describe the resistance used by Lippelt since the pressure and volume relationship was not linear. From a pressure volume graph in his paper the resistance appears to be 160 mm. H_2O at a rate of flow of approximately 220 c.c./second.

TABLE II. EFFECT OF RESISTANCE ON VENTILATION

	Tidal Vol. c.c. BTPS	Respiratory rate	Minute Vol. c.c. BTPS
Control	832	12	9710
R-1	947	10.1	7508
Recovery	856	12.5	10342
Control	802	13	10148
R-2	1219	7.4	8829
Recovery	844	13.9	9610

A continuous record was made with the Benedict Roth metabolism apparatus, consisting of five minutes control, five minutes on R-1 and five minutes recovery. The same procedure was repeated for R-2. The values are averages for all five subjects.

This prolongation of the respiratory phases is accompanied by a decreased peak flow. Although considerable extra pressure is developed by the respiratory muscles when resistance is added (Table I), it is not enough to maintain the normal flow pattern. The tidal volumes, as determined by integration of four cycles for each individual, showed, on the average, little change with added resistance. The mean rate of flow (total ventilation) consequently decreased. In another series of experiments the tidals were measured from tracings obtained with a recording spirometer. By this method an increased tidal volume with added resistance was noted (Table II). This increase was not enough to compensate for the slower rate, however, and the total ventilation showed a significant decrease. Silverman[9] obtained similar results in a controlled study on a large number of subjects with resistance on inspiration under working conditions. He suggests that this is compensated for by an increased oxygen utilization. The

TABLE III. THE EFFECT OF RESISTANCE (R-2) ON ALVEOLAR GAS EXCHANGE

Averages from measurements on five subjects

	pCO_2	pO_2	R.Q.
Control	40.6	99.2	0.80
R-2	42.4	96.1	0.78
Recovery	39.9	100.9	0.82

resistances used by Silverman were not high enough to show any physiological effects when the subjects were sedentary; only under working conditions did their effect become significant. Silverman's highest resistance was 0.11 mm.H_2O/c.c./sec. The resistance with R-1 in the circuit in the present study was 0.14 mm.H_2O/c.c./sec. but was present during expiration as well as inspiration.

The observed decrease in total ventilation indicated retention of carbon dioxide during resistance breathing, unless the resistance in some way decreased the physiological dead space. Consequently the alveolar pressures of carbon dioxide and oxygen were determined for the five subjects. End expiratory samples were taken every three minutes during a control period, a period on R-2 and a recovery period, each period being twelve minutes in length. The samples were subsequently analyzed for CO_2 by a Cambridge Instrument Company thermal conductivity meter and for O_2 by a Pauling tensimeter. All subjects showed an increase in alveolar pCO_2 and a decrease in the pO_2. The average values are shown in Table III. The increase in alveolar pCO_2, together with the lowered respiratory quotient, demonstrates the retention of CO_2 during resistance breathing. During recovery the converse situation holds as CO_2 is blown off. A rise in CO_2 tension during breathing against strong resistance has also been observed by Davis, Haldane and Priestley.[3]

The retention of CO_2 during resistance breathing indicates a compromise by the body. The body tolerates some rise in CO_2 tension in preference to expending the effort that would be required to keep it at the original level.

WORK AND EFFICIENCY OF BREATHING ON ADDED RESISTANCE

As resistance is added to the flow of air during respiration, an increased inspiratory and expiratory effort is required to maintain adequate ventilation. When resistance is external and artificially produced, the increased force required is manifested in higher mouth pressures. Since the simultaneous pressure drop and volume flow across the resistance can be easily measured, the extra external work of breathing can be calculated. When determined by this method, the extra work is that additional amount required to force the air through the resistance.

In order to determine the extra work required for breathing through the added resistance, it was necessary to determine the flow and pressure relationship at intervals during the respiratory cycle. The rate of flow curve and pressure curve were reproduced on graph paper, maintaining the same relationship as existed on the original records. The pressure and flow curves for each phase of a respiratory cycle were divided into five parts by constructing vertical lines at equal inter-

vals along the time axis. The volume represented by each of the five areas under the flow curve was determined by integration with a planimeter.

It is also possible to estimate the potential energy which is stored up by the elastic forces of the lung and chest during inspiration and which is available to assist expiration. This has been done by use of the equation

$$W = \frac{KV^2}{2}$$

where W is the potential energy, V the tidal volume and K the slope of the relaxation pressure curve. The value for K was taken as 1 mm.Hg/94 c.c. from Rahn, Otis, Chadwick and Fenn.[7] Results of such calculations are included in Table IV. The potential energy exceeds the extra work required

TABLE IV. EXTRA WORK REQUIRED TO INSPIRE AND EXPIRE A KNOWN TIDAL VOLUME ON THE CONTROL, R-1 AND R-2. MEANS OF VALUES FROM FIVE SUBJECTS

Resistance	Extra Work in Gram Centimeters		Tidal Volumes in Cubic Centimeters	Elastic Potential Energy Available for Expiration in Gram Centimeters
	Inspiration	Expiration		
Control	3660	2628	880	5550
R-1	5500	5228	970	6720
R-2	18000	12180	990	7040

The inspiratory work is consistently larger than the expiratory work. The inspiratory muscles develop a higher rate of flow than the expiratory muscles, and therefore a higher pressure, which accounts for the additional work during inspiration. It must be remembered that the inspiratory phase is always shorter than the expiratory phase of respiration. When the time element is considered, the extra work of inspiration appears to be the compensation demanded for the reduced time.

When pressure is plotted against accumulated volume for a complete respiratory cycle (considering inspiratory increments negative and expiratory increments positive in sign), a closed loop is formed, the area of which is equivalent to the extra work done in overcoming the resistance. Figure 3 is such a plot based on averages of measurements on two respiratory cycles of each of the five subjects. The values for extra work required to overcome the resistances were obtained by planimetric integration of these curves and are shown in Table IV.

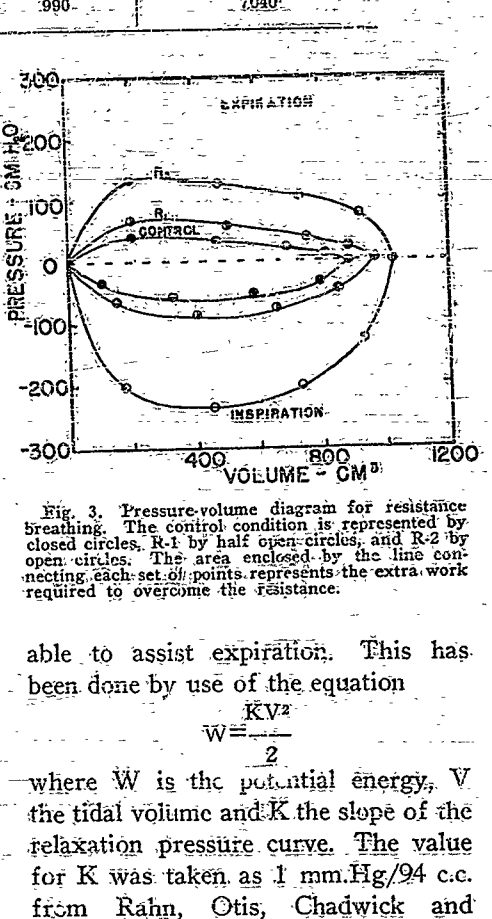

Fig. 3. Pressure-volume diagram for resistance breathing. The control condition is represented by closed circles, R-1 by half open circles, and R-2 by open circles. The area enclosed by the line connecting each set of points represents the extra work required to overcome the resistance.

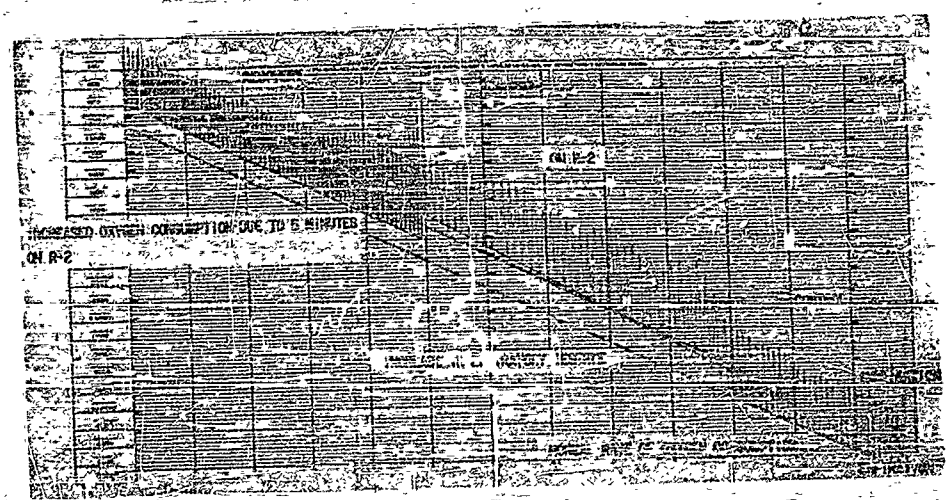

Fig. 4. Typical record showing extra oxygen consumption due to R-2. Curve reads from right to left. The difference between the original slope and the slope of the fine dotted line represents the extra oxygen consumption. The vertical distance between the extrapolation of the original slope and the heavy line represents the increase in expiratory reserve.

TABLE V. EXTRA WORK, EXTRA OXYGEN CONSUMPTION AND MECHANICAL EFFICIENCY OF BREATHING ON R-2

Condition	Extra Work per Minute		Extra O_2 Consume per Minute		Efficiency
	Gram Centimeters	Calories	Cubic Centimeters	Calories	
Resistance in both phases	196,310	4.59	29.4	141	3.3%
Resistance in inspiration only	123,973	2.88	20.8	100	2.9%
Resistance in expiration only	74,175	1.74	23.2	111	1.6%

for expiration for control and R-1. However, for the heavy resistance, R-2, the potential energy is one-fourth to three-fourths (the average for all subjects being approximately one-half) the amount required for expiration. Furthermore, some potential energy is necessary to overcome the natural internal resistance to expiration.

From this comparison it appears that a resistance somewhere between that of R-1 and R-2 (i.e., between 75 and 200 mm. H_2O resistance at a rate of flow of 520 c.c./sec.) exists, for which the potential energy would equal the expiratory work. If there were no demand on the respiratory mechanism to maintain an expiratory time within certain limits, the expiratory muscles would not need to become active until the expiratory work was equal to the potential energy. The potential energy remains the same for a given volume, while with added resistance the expiratory work increases and the time to reach maximum flow decreases. This suggests that expiration changes from a relatively passive act to an active expiration before ex-

piratory work becomes equal to potential energy. This conception coincides with the subjective sensation while breathing on a light resistance. The active expiration is necessary to maintain the total expiratory time within adequate limits.

The efficiency of the extra work done in overcoming added respiratory resistance was estimated by the following procedure. The mean value determined for each individual for the extra work per tidal volume was multiplied by the frequency of breathing to obtain the work per minute. In a separate experiment in which the subject breathed from a Benedict Roth metabolism apparatus first without and then with the resistances, the extra oxygen consumption was estimated (Fig. 4). By dividing the extra work by the extra oxygen consumption, the efficiency was obtained. The results are shown in Table V.

The extra oxygen consumption with R-1 was so small that it could not be accurately measured, and no values are reported. With R-2 the extra oxygen consumption was on the average 29 c.c. per minute, which is comparable with the 6 per cent increase reported by Anthony and Lent[1] for subjects breathing on a resistance of approximately the same magnitude. The efficiency for the extra work with R-2 varied from 1.7 per cent to 5.3 per cent among the different subjects. The average is 3.3 per cent, a figure of the same order of magnitude as the estimate of 5 per cent for the mechanical efficiency of normal breathing given by Rahn et al.[8]

In another series of experiments, measurements of the extra work and extra oxygen consumption were made in the same manner as described above but with the resistance inserted on inspiration only and on expiration only. Averages of the measurements on the five subjects together with the calculated efficiency of the extra work are shown in Table V.

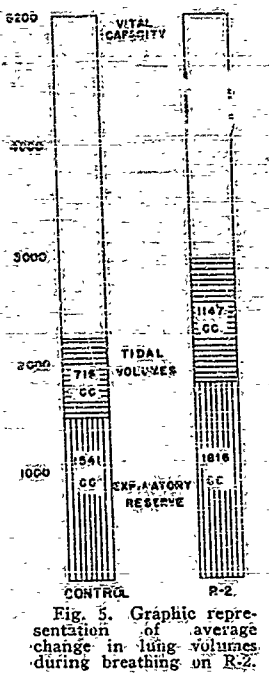

Fig. 5. Graphic representation of average change in lung volumes during breathing on R-2.

For all subjects, the mechanical efficiency of the extra work was less when the resistance was in expiration only than when it was in inspiration only, the average values being 2.9 per cent for inspiration and 1.6 per cent for expiration. This finding is of particular interest in view of Silverman's[11] statement that exercise tolerance is less with expiratory resistance than with inspiratory resistance of the

same magnitude. It has also been observed by Lent[4] that expiratory resistance is subjectively more unpleasant than is inspiratory resistance.

With resistance present in only one phase of respiration, most subjects showed no change in expiratory reserve as judged from the oxygen consumption records. On the other hand, when resistance was present in both phases, all subjects showed an increase in expiratory reserve ranging from 186 to 351 c.c. (Fig. 5). This situation favors the expiratory muscles, since they are working at a greater length than normal, and may account for the fact that the efficiency is greater when resistance is present in both phases than when it is present in inspiration only or in expiration only.

In the above discussion it is assumed that the only extra work done was that required to force air through the resistance. It is possible that some change in the internal viscous work (movement of blood and viscera, e.g.) may occur, but it seems unlikely that this would be of any considerable magnitude.

EFFECT OF RESISTANCE ON THE BALLISTOCARDIOGRAM

Since cardiac output is known to vary during inspiration and expiration,[8,12] it was considered important to investigate the effect of respiratory resistance on the ballistocardiogram.

The ballistocardiograph table used was designed by Blair,[8] and the method of recording was that of Brown and Pearson.[2] The only variation from the usual procedure was a provision for suddenly switching into the breathing circuit the heavy resistance R-2. A control record was taken, and without stopping the record the resistance was switched into the circuit. This method gave the initial effects on the ballistocardiogram complexes of breathing on resistances. After five minutes on the resistance the record was again taken and continued while the resistance was switched off, to show the initial effects on the complexes of suddenly being relieved of the resistance. Another record was taken after an additional five minutes.

The complexes with the largest amplitude occurring during inspiration were selected, the I and J peaks measured,[12] the heart rate determined from the cycle lengths, and an inspiratory cardiac output determined. The smallest complexes occurring during expiration were similarly used to compute an expiratory cardiac output. The cardiac output was also determined for one complete respiratory cycle. These three determinations were made for each condition of the experiment: control, immediately after switching on R-2, R-2 after five minutes, beginning of recovery, and recovery after five minutes for all subjects. Starr's[12] height formula was used in each case.

As calculated from complete respiratory cycles, the cardiac output of all but one subject showed an increase immediately after switching in the resistance. At the end of five minutes on the resistance, however, it was less than normal in four of the five subjects. Averaged changes are shown in Table VI. Since no change, even in individual subjects, was greater than 8 per cent, the effects of the resistance on the over-all cardiac out-

TABLE VI. AVERAGE CARDIAC OUTPUT FOR ALL SUBJECTS AS CALCULATED FROM THE BALLISTOCARDIOGRAMS TAKEN DURING PERIODS OF CONTROL, RESISTANCE AND RECOVERY BREATHING

	Maximum Inspiratory		Minimum Expiratory		One Respiratory Cycle	
	c.c./min.	Per Cent Change from Control	c.c./min.	Per Cent Change from Control	c.c./min.	Per Cent Change from Control
Control	4278	—	3559	—	3933	—
1st minute on R-2	4658	+8.9	3304	−7.6	4069	+3.5
5th minute on R-2	4357	+1.8	3070	−13.7	3762	−4.4
1st minute of recovery	4334	+1.3	3492	−1.9	3820	−2.9
5th minute of recovery	4332	+1.8	3637	+2.2	3970	+ .9

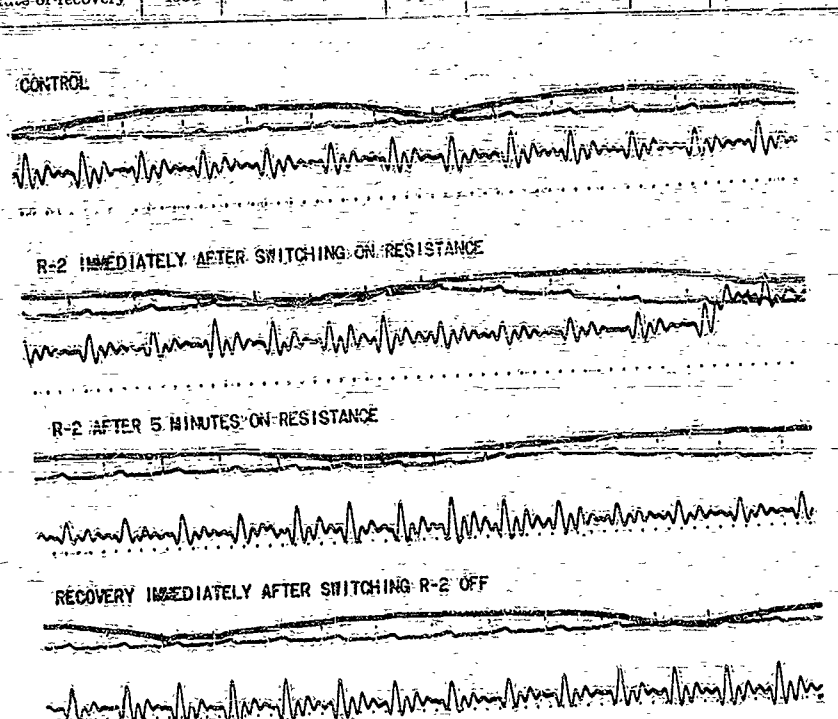

Fig. 6. Effects of R-2 on the ballistocardiogram. The upper curve in each case is the pneumograph tracing in which a downward deflection represents inspiration. Below this is the electrocardiogram and the ballistocardiogram. Time line intervals are 0.2 seconds.

put are not regarded as being highly significant.

Although changes in the total cardiac output over a respiratory cycle are small, the variation between expiratory and inspiratory outputs is striking. As shown in Figure 6, the difference between the largest inspiratory beat and the smallest expiratory beat becomes greater as soon as the resistance is switched into the circuit. This condition persists as long as the resistance is present and immediately returns toward normal when the resistance is removed. The average inspiratory-expiratory variations are

shown in Table VI. Cardiac minute volumes have been used rather than stroke volumes, in order that any variation in the heart rate as determined from the cycle lengths would also be reflected.

SUMMARY

1. The respiratory patterns are altered by added resistance. The total time of each phase of respiration is increased, the maximum rate of flow decreases, the time required to reach maximum rate of flow decreases (until resistance becomes very high), the mean rate of flow decreases and the peak inspiratory and expiratory pressures increase. The shape of the expiratory pattern changes from a relatively triangular shape to one more nearly rectangular, and the inspiratory pattern shows a smaller change in the same direction.

2. The inspiratory work required to overcome the resistance is consistently higher than the expiratory work. The average efficiency for the extra work of a complete respiratory cycle on a resistance of 0.385 mm. H_2O/c.c./sec. was 3.3 per cent.

3. The expiratory reserve increased 275 c.c., on the average, when breathing on a resistance of 0.385 mm. H_2O/c.c./sec. This change in expiratory reserve favors the muscles of expiration.

4. Breathing on resistance decreases total ventilation and brings about an increased alveolar pCO_2 and a decreased pO_2.

5. The ballistocardiograms showed an increased cardiac minute volume during inspiration and a decrease during expiration on a resistance of 0.385 mm.H_2O/c.c./sec. The cardiac minute volume as determined from complete respiratory cycles decreased 4 per cent after five minutes on the resistance.

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A NEW METHOD FOR THE RECORDING OF THE PRESSURE-VOLUME DIAGRAM OF THE CHEST AND LUNGS BY MEANS OF A CATHODE RAY OSCILLOGRAPH

by

A. B. DuBois[1] and B. B. Ross

Hitherto the pressure-volume relationships of the chest and lungs have been measured and plotted by time consuming methods. The purpose of this paper is to report the simultaneous use of both axes on the cathode ray oscillograph for direct production of these curves. The equipment used to measure the elastic, viscous, and inertia factors in the work of breathing consists of one or two strain guages, a pneumotachometer, spirometer with potentiometer attached to the pulley for recording volume, and a Dumont 304 H cathode ray oscillograph. It is also convenient to use an 'Electrodyne Stimulator' on the Z axis to interrupt the cathode beam at intervals of a tenth of a second.

The pressure-volume curve of the chest of a normal human subject (Fig. 1) was generated using the above equipment in conjunction with a Drinker respirator, which provided the force necessary for breathing as the subject relaxed. Either the subject or the spirometer may be placed in the respirator; in the latter case a Sanborn 'Waterless' metabolism tester is placed inside the iron lung and its tubing let out through a board covering the hole for the head. 'Transthoracic pressure'[2] is measured by a strain guage which is connected to the X axis input terminals of the oscilloscope. Volume is recorded on the Y axis of the oscilloscope. The elastic constant of the chest is found by drawing a line through the maximum and minimum volume points of the curve. The extra pressure used in overcoming nonelastic resistance is the horizontal distance from this elastic line to the curve. The flow at this instant is found by measuring the change in volume occuring between two of the time marks on the curve. The area of the loop represents the viscous work of breathing.

Other relationships that have been demonstrated satisfactorily on the oscilloscope are: (1) Flow at the mouth on the Y axis, pressure in a ureteral catheter inserted as far as it will go into a bronchus on the X axis. This gives a fair approximation of the relationship between alveolar pressure and gasflow. (2) Intrapleural pressure on the X axis versus volume on the Y axis gives the elastic and viscous forces of the lung during normal or artificial respiration. (3) If the alveolar pressure is opposed to the intrapleural pressure on a differential pressure guage (X axis), volume on the Y axis, one may obtain the elastic curve of the lung. (4) With flow at the mouth on the Y axis and pressure on the X axis, phase shifts appear as elliptical, or circular (90° shaft), loops on the oscilloscope when rapidly oscillating pressures are applied at the mouth. This yields some idea of the inertia of the chest. (5) Response to a sudden pressure wave is shown by triggering off a single sweep on the oscilloscope, with pressure or flow at the mouth on the Y axis.

1 This work was done during the tenure of a Life Insurance Medical Research Fellowship.

2 Pressure difference between mouth and atmosphere surrounding the chest, as used by Dr. A. C. Burton.

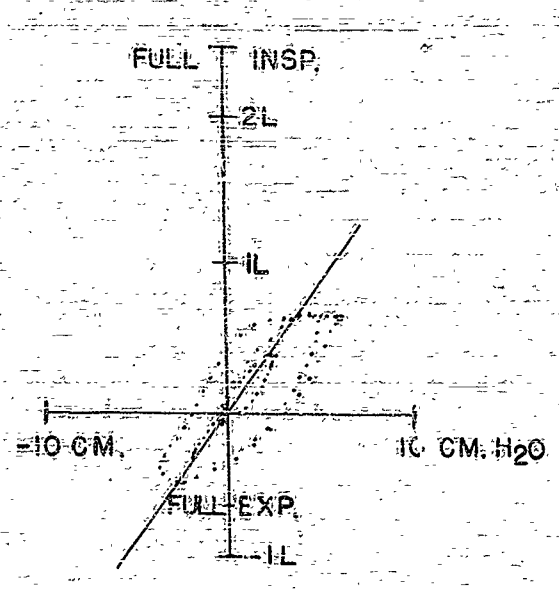

Figure 1

Three pressure-volume curve of the chest of a relaxed human subject, photographed on a cathode ray oscillograph. The beam is interrupted at tenth of a second intervals to permit measurement of rate of gasflow. For interpretation, see text.

The simultaneous use of the X and Y axis of the cathode ray oscilloscope for studying the pressure-gasflow relationship of the nasopharynx has been pointed out by J. C. Lilly (1). The experience of this laboratory is that the method is rapid and versatile and facilitates study of all the factors in the mechanics of breathing in man as well as animals.

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THE PNEUMATIC BALANCE RESUSCITATOR

by

Hermann Rahn, Arthur B. Otis, Mary Hodge, Manuel Brontman,
James Holmes and Wallace O. Fenn

March 5, 1945

This investigation was undertaken at the request of Col. Lovelace in January and February 1945 using one of the early models of the Burns resuscitator (P.B.R.) made at the Aero-medical Laboratory at Wright Field. The object was to study its mechanical and physiological characteristics and its suitability for use by the Air Force as a resuscitator. The following is an abbreviated version of the report submitted.

1. PRELIMINARY EXPERIMENTS

Observations were made on 6 normal subjects, 5 of them in the supine and 1 in the sitting position. Arrangements were made to collect the expired air and pass it through a continuously recording gasometer. Samples of the expired air were taken at frequent intervals and analyzed for oxygen and carbon dioxide. The measurements of the total ventilation were fallacious because some air leaks through the valve from the inlet tube during expiration. This also invalidates alveolar air samples taken from the mask. The subjects breathed quietly before each experiment for 15 minutes with the mask attached but without pressure. Recordings were made for the last 10 minutes of this period. A pressure of 22 cm of water was then applied and the subject was instructed to relax and sleep if possible.

In 5 out of 6 cases the R. Q. increased when pressure breathing began and subsequently declined. This indicates a blowing off of CO_2 for a short time and is consistent with a slight hyperventilation. On the whole the changes in the rate of oxygen consumption were insignificant in 4 cases and decreased about 40 cc per minute in 2 cases. Of the 6 subjects, 2 fell asleep for 8 and 9 minutes respectively. In both subjects this was accompanied by a decrease in oxygen consumption, CO_2 output and R.Q. and an increase in the frequency of breathing. Other subjects showed no consistent change in frequency when pressure was applied.

2. SECOND SERIES OF EXPERIMENTS

In this series of experiments the air passed through a pressure demand regulator into the mask fitted with the PBR Burns regulator. From the mask the expired air passed through two 3-way stopcocks to a large spirometer. To obtain alveolar air for analysis the demand regulator was shut off thus permitting the air in the inlet tube to fall to atmospheric pressure. The subject then expired maximally through the outlet tube and the alveolar air was trapped between the two stopcocks where it

The work was supported by Contract OEM-cmr between the University of Rochester and the Office of Scientific Research and Development.

TABLE 1

Summary of Data on Normal Subjects on the Pneumatic Balance Resuscitator

Time min.	Mask Pressure at end of Inspiration cm. H_2O	Alveolar CO_2 mm. Hg.	Ventilation † l/min.	Leak † l/min.	CO_2 Output cc./min.	Subject
0-5	0	39.4*	6.1	0	220	Otis supine
7-12	20	33.3*	7.1	2.9	222	
14-19	20	30.6*	7.52	2.58	217	
21-26	20	30.6*	7.38	2.82	204	
0-5	0	42.0*	7.7	0	274	Culp sitting
7-12	18	37.2*	8.58	2.62	278*	
15-20	18	32.6*	8.54	2.16	246*	
22-27	18	35.6*	7.94	2.26	234*	
0-5	0	44.2	5.88	0	248	Mitchell supine
7-12	20	35.6*	7.82	3.55	264	
15-20	20	-	-	-	210	
23-28	20	35.4*	8.08	3.62	210	
0-5	0	43.4	6.96	0	279	Brontman sitting
7-12	18	26.6*	11.84	0.96	378	
22-27	18	28.6*	9.33	2.57	274	
0-5	0	46.0	5.46	0	234	Holmes sitting
7-12	18	31.4	8.98	3.42	284	
20-25	18	33.5	-	-	-	
0-5	0	-	6.66	0	210	Mitchell sitting
7-12	18	34.8	-	-	-	
19-26	18	34.4	8.40	1.5	198	

All volumes are calculated for 0°C, 760 mm., dry (S.T.P.)
† Calculated except for normal run.
* Haldane method of analysis.

was sampled. The correct alveolar ventilation, Va, was then calculated from the CO_2 output and the alveolar fCO_2 by the equation.

$$Va = \frac{CO_2 \text{ output}}{fCO_2}$$

The dead space for each individual with the mask attached was measured in the usual way; the values obtained in 5 subjects varied from 189 to 218 cc. With these values the tidal volume and total ventilation could be calculated from Va and the frequency of breathing. The difference between this calculated ventilation and the value determined from the spirometer readings is a measure of the leak through the valve which occurs during expiration.

The results of these experiments are shown in Table 1. In all cases the alveolar pCO_2 fell during the P.B.R. "resuscitation," the average change being from 43 to 32.9 mm. At the same time the average calculated minute volume rose from 6.46 to 6.46 liters per minute (B.T.P.S.). In 5 of the subjects the CO_2 output showed an increase from an average normal of 251 cc per minute to an average value of 265 cc per minute for the first period after the application of pressure. In later periods it declined to the normal level or fell below it.

3. MEASUREMENT OF LUNG VOLUMES WHILE BREATHING THROUGH THE P.B.R.

Since the mask pressure while breathing through the P.B.R. is always greater than the ambient pressure it is reasonable to expect that the breathing will occur at a lung volume somewhat larger than the normal. To demonstrate this a series of experiments was tried on 8 subjects, each breathing through the P.B.R. at 3 different line pressures, first in the supine and then in the sitting position. A gasometer was included in the inlet tube; from the movements of the pointer both the tidal volume and the magnitude of the leak during expiration could be measured. At 5 minute intervals at each pressure the inflow was turned off and the line pressure reduced to atmospheric level by turning a 3-way cock at the end of a normal inspiration. The subject then expired maximally into a small spirometer simultaneously brought into connection with the outlet tube by the turn of another stop cock. The spirometer reading gave the value of the expiratory reserve plus the tidal volume.

The results of these experiments are shown in Table 2. The data show that with an increase in line pressure from 8 to 20 cm. of water there was an increase in the minute volume of the ventilation, the tidal volume and the expiratory reserve and a decrease in the frequency of breathing. All of this is in accord with expectations. Since the ventilation increased there must have been some decrease in the alveolar pCO_2 but it was not sufficient to produce any symptoms of acapnia.

4. THE EFFECT OF THE P.B.R. ON THE VENOUS PRESSURE

The venous pressure was recorded by an optical membrane manometer connected by a lead tube to an 18 gauge needle inserted in the cubital vein. Simultaneous records of mask pressure were taken by a similar manometer. Typical records are shown in Fig. 1 where the thinner line represents venous pressures and the heavy line mask pressures. Both cardiac and respiratory waves are seen.

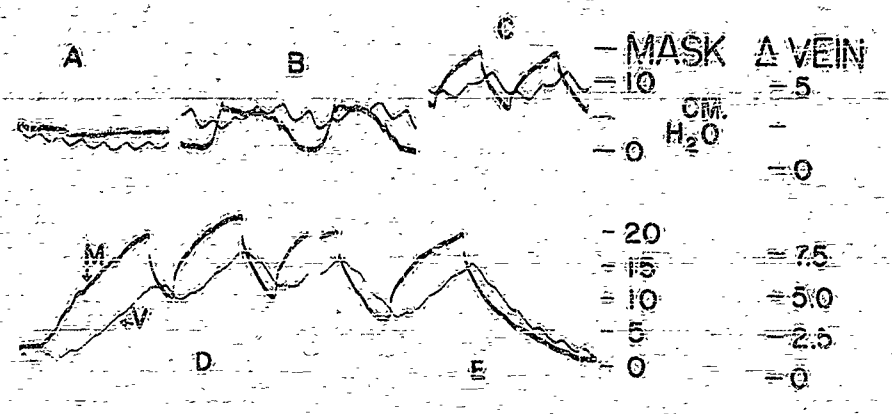

Figure 1

These records show the simultaneous variations in mask pressure and in peripheral venous pressure of a subject breathing on the P.B.R. The venous pressure record is the thinner of the two tracings. The zero of the venous pressure scale is the normal venous pressure of the subject. One second = 5.4 mm. on all records.

A. This record was taken during normal breathing with the mask lifted slightly from the face so as to remove any hindrance to expiration.

B. Taken with the mask in position but with no line pressure. Note the considerable resistance to expiration.

C. Section of a record with the P.B.R. set at 16 cm. Actual peak mask pressure is about 15 cm.

D. Record at the maximum pressure setting of the P.B.R. showing the response of mask and venous pressure at the time when line pressure is turned on.

E. Same as D, but showing the response when the line pressure is turned off.

TABLE 2

Average Lung Volumes of 8 Subjects on the Pneumatic Balance Resuscitator at Different Pressures and in the Sitting and Supine Positions

	Regulator setting* cm.H_2O	Actual Line Pres. cm.H_2O	End of Inspiration cm.H_2O	End of Expiration cm.H_2O	Expiratory Reserve liters	Tidal Vol. liters	Rate/ min.	Ventilation l/min.	Vital Capacity liters
	22	34-22	18	7	1.86	1.07	10	10.90	
sitting -	16	22-15	12	5	1.57	.63	12	8.55	4.1
	12	17-11	8	4	1.51	.54	16	8.45	
	22	34-25	20	8	1.22	1.03	12	12.00	
supine -	16	24-18	14	4	1.11	.81	17	10.00	3.9
	12	19-13	10	4	0.95	.40	20	7.60	

* The regulator is caliorated in terms of mask pressure which is supposed to be 75% of the intake line pressure. The large recorded fluctuations in the line pressure are due to the resistance of the wet test meter which did not feed air fast enough to keep up the intake pressure during inspiration.

Lung volumes at S.T.P.D. (760 mm., 0°C. dry).

Careful measurements of the records taken at 10, 16, and 22 cm. of water show that on the average venous pressure rises 40% as much as the pulmonary pressure but lags behind the latter due to the distensibility of the veins between the heart and the point of measurement. The difference between the venous and pulmonary pressure changes is due partly to pressure absorbed by the distended lung and partly to incomplete filling of the veins. The large variation in mask pressure shown in Fig. 1B when the line pressure was zero indicates that the resistance of the valve is considerable and suggests the importance of removing the mask promptly when the inlet pressure fails.

At pressures less than 16 cm of water the subjects frequently experienced some air hunger and tended to "lead" the machine in order to increase the flow. This was indicated in records like those of Fig. 1 by the resulting pressure changes in the mask.

5. CHANGES IN CARDIAC OUTPUT AS MEASURED BY THE BALLISTOCARDIOGRAM

The subject reclined on the ballistocardiograph table for 10 minutes before a normal record was taken. Then the mask with maximum pressure of 22 cm. of water was applied for 7 minutes and a record was taken at the end of this time. In the calculation of the stroke volume, no attempt was made to determine actual volumes but merely the relative change that occurred when the resuscitator was in use. Calculations were made according to Starr's (1939)* wave-height formula.

All 5 subjects showed similar responses, i.e. a reduction in cardiac output (averaging 27%) as shown in Table 3. This reduction can be attributed to the retardation of venous return to the heart due to the positive pressure produced by the resuscitator.

TABLE 3

Reduction of Cardiac Output on the P.B.R.
Ballistocardiographic Measurements

Subject	Heart Rate		Relative Stroke Vol.		Rel. Cardiac Output		% Reduction
	Normal	Pressure	Normal	Pressure	Normal	Pressure	in C.O.
Holmes	68	71	6.71	4.75	456	337	26%
Mitchell	81	72	5.44	3.84	440	276	37%
Rahn	78	68	4.67	2.99	365	279	24%
Culp	56	66	6.39	3.78	358	249	30%
Horvath	71	67	4.32	3.78	306	253	17%
Average	71	74	5.51	3.83	385	279	27%

Stroke volumes and cardiac output are expressed in arbitrary units.

A similar reduction of 14% in cardiac output was found by the same method in 6 subjects breathing through the pneumolator of the General Electric Xray Corp. (Our report, C.A.M. No. 2492; also Otis et. al. 1946).

DISCUSSION

After completion of our work we received a report of similar work undertaken by Olson at the Aero-medical Unit of the Mayo Clinic. Their findings were in general agreement with our own but two points deserve special mention. They found no evidence of diminished alveolar pCO_2 except in one subject at 20 cm. of water pressure. The increased ventilation which they report may have been due to a leak into the mask during expiration. They found a significant decrease in the rate of oxygen consumption while breathing on the P.B.R. and suggest that this decrease may represent the cost of voluntary breathing movements without the assistance of the P.B.R. We do not feel that our own observations have established any such decrease in oxygen consumption but they do not exclude this as a possibility.

The increase in venous pressure with increase in pulmonary pressure is well known from other work (Holt, 1943; Barach 1938 and 1943, Otis, Rahn and Fenn, 1946). In the present case the rise in venous pressure is somewhat less than it would have been if more time could have been allowed to reach equilibrium between the venous pressure and the pulmonary pressure.

On the whole we found the instrument very satisfactory for use as a resuscitator. It is small in size, effective in operation, and offers little in the way of moving parts which can get out of order.

CONCLUSIONS

1. When used on normal conscious persons, the P.B.R. gives very comfortable ventilation with pressures of 10cm. of water or above. With lower pressures, passive ventilation leads to air hunger.

2. With peak pressures of 22cm. of water there is an increased ventilation and a fall of alveolar carbon dioxide tension to about 30 mm. but no obvious symptoms of acapnia.

3. During sleep the P.B.R. chatters a good deal giving a high mask ventilation but a subnormal alveolar ventilation. This indicates that the pressure available will not force open a closed glottis and emphasizes the importance of keeping the air way open artificially in case any chattering is observed. In 2 subjects receiving artificial respiration on the Drinker Respirator a similar marked decrease in ventilation was observed during sleep.

4. The venous pressure increases in response to the increased pulmonary pressure on the P.B.R. The rise in venous pressure is 50% of the rise in pulmonary pressure.

5. Measurements of the cardiac output by the ballistocardiograph indicates an average decrease in output of 27% with a peak mask pressure of 22cm. of water.

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MECHANICAL BEHAVIOUR OF THE BURNS PNEUMATIC BALANCE RESISCITATOR

by

Wallace O. Fenn, Arthur B. Otis, and Hermann Rahn

September 30, 1945

1. INFLOW RESISTANCE

Air was allowed to flow through a gas meter and then through the PBR without any mask attachment. The line pressure was constant and the pressure on the mask side of the PBR was zero. The flow in liters per minute was found to be proportional to the square root of the pressure gradient (in this case the line pressure). This shows that the flow through the small orifices is turbulent in nature. Similar data were obtained at 34000 and 17000 feet. The results are shown in Fig. 1.

2. OUTFLOW RESISTANCE

The mask end of the PBR was attached through a gas meter to a constant head of pressure and the measurements were made of the flow at different pressures. Again the flow was found to be proportional to the square root of the pressure. Measurements were also made at 34000 and at 17000 feet. The results are given in Fig. 2.*

3. EFFECT OF ALTITUDE ON INFLOW AND OUTFLOW RESISTANCE

For turbulent flow, the flow should be inversely proportional to the square root of the density or inversely proportional to the square root of the barometric pressure. Using the same observations described in 1 and 2 above it was possible to test this theory by plotting the flow obtained at a given head of pressure against the reciprocal of the square root of the barometric pressure. This is done in Fig. 3 for the inflow resistance and Fig. 4 for the outflow resistance. The flow is found to increase with altitude and the data are reasonably well represented (except 1 point in Fig. 4) by straight lines through the origin as the theory of turbulent flow demands.

4. EQUATIONS FOR INFLOW AND OUTFLOW THROUGH THE PBR

From the data presented in Figs. 1 to 4 it may be concluded that the following equations represent the inflow and outflow through the PBR at different altitudes.

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* The outflow constant is partly due to the leakage which occurs in our instrument between the outflow housing of the PBR and the upper disc (on the mask side). Some air escapes from the valve even when the inflow and all the outflow parts are blocked. A small gasket at this point might be useful. This leak could increase the outflow constant about 0.4 corresponding to an escape of 1.2 liters per minute at a pressure of 9 cm. There must be some error due to this in our determination of frequencies and ventilations.

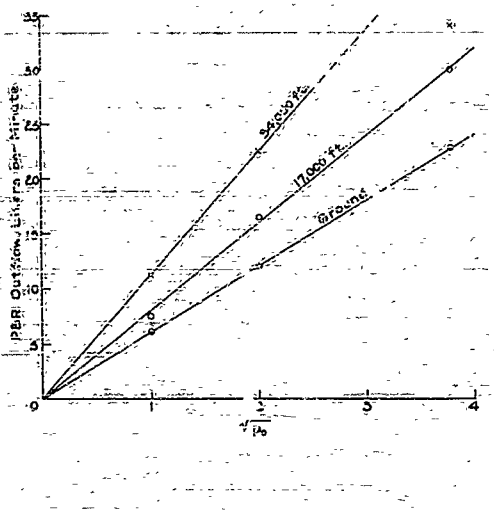

Figure 1

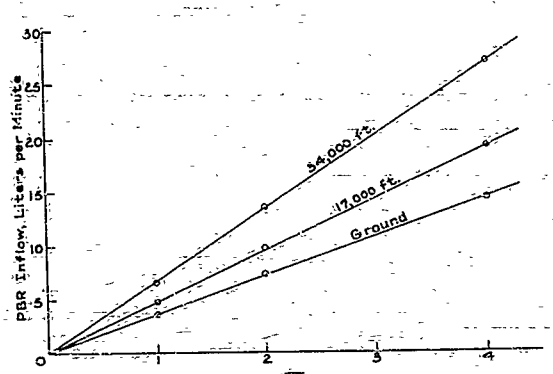

Figure 2

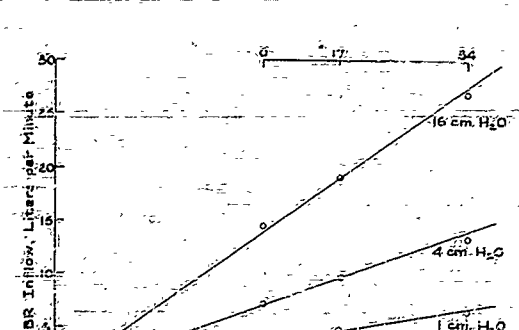

Figure 3

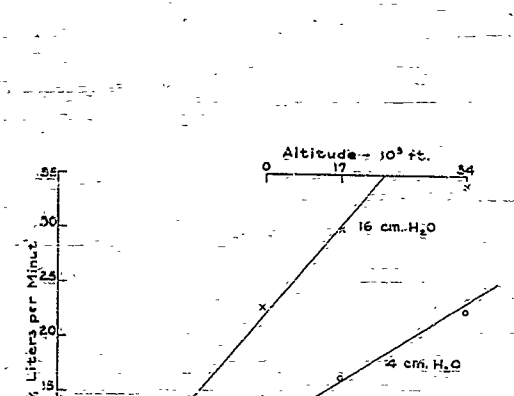

Figure 4

$$\text{Inflow} = \frac{96\sqrt{p}}{\sqrt{B}} \qquad \text{(equation 1)}$$

$$\text{Outflow} = \frac{164\sqrt{p}}{\sqrt{B}} \qquad \text{(equation 2)}$$

Flow is expressed in liters per minute; p is the pressure gradient in cm. H_2O and B is the barometric pressure in MM Hg.

It follows from these equations that for the same pressure gradient the outflow is 164/96 or 1.7 times as rapid as the inflow. This at least applies to the particular instrument available at this laboratory.

5. THE EFFECT OF LINE PRESSURE ON THE FREQUENCY OF CYCLING

A. Theoretical

Consider a system in which the line pressure is held constant and the pressure in the lung increases linearly with volume of gas which flows into it. This is approximately the case in the human lung over the physiological range

p_o = line pressure in cm. H_2O
p = pressure in the mask and lung at time t in cm. H_2O
Q = the volume of air delivered to the lung at time t in liters
$p = AQ$ (equation 3)

where A is a constant depending upon the elasticity of the lungs.

$$\frac{dQ}{dt} = k\sqrt{p_o - p}$$

$$\frac{dp}{dt} = A\frac{dQ}{dt}$$

$$\frac{dp}{dt} = Ak\sqrt{p_o - p}$$

On integration this gives*

$$2\sqrt{p_o - p} = -Akt + C$$

When $t = o$, $p = .25p_o$ $\quad \therefore C = 2\sqrt{.75p_o}$

When $p = .81\,p_o$

$$2\sqrt{.19p_o} = -Akt + 2\sqrt{.75p_o}$$

$$t = \frac{.86\sqrt{p_o}}{Ak} \qquad \text{(equation 4)}$$

In this equation t is the time necessary for the pressure in the mask to rise from $0.25p_o$ to $.81\,p_o$ these being the values found in the instrument at our disposal. If the inspiration time is a constant fraction of the total cycle time (64% in our measurements) then the total cycle time is t/0.64 and the frequency per minute is $\frac{64}{t}$ if t is in minutes (as it is when A and k are in liters and minutes).

* We are indebted to Dr. H. A. Blair for assistance with this equation.

TABLE I

PBR in Simulated Lung – Elastance Only

Effect of line pressure on the PBR

(1) line pr. min.	(2) line pr. max.	(3) lung pr. min.	(4) lung pr. max.	(5) cycle duration	(6) Frequency on record	(7) Frequency counted	(8) p in lung	(9) tidal vol.	(10) Ventilation meter record	(11) Ventilation meter record	(12) sq. root of min. line pr.	(13) inspiration in % of cycle time	(14) $\frac{p}{p_o} \times 100$ min.	(15) $\frac{p}{p_o} \times 100$ max
cm H_2O	cm H_2O	cm H_2O	cm H_2O	sec.	min.	min.	cm H_2O	cc	lit/min	lit/min		%	%	%
28.5	30.6	6.7	22.4	9.75	6.15	5.7	15.7	1660	8.8	10.2	5.35	67	21.9	79
22.3	24.2	6.2	18.7	8.7	6.9	6.1	12.5	1325	8.6	9.1	4.74	67	25.6	84
18.2	19.8	5.2	14.8	8.4	7.15	7.2	9.6	1030	7.2	7.4	4.26	61	26.2	81
14.2	15.5	4.3	11.7	7.3	8.2	8.2	7.4	778	6.2	6.4	3.76	65	27.7	82
10.8	12.1	3.0	8.7	6.4	9.45	9.4	5.7	604	5.5	5.7	3.29	62	24.8	80
6.5	7.7	2.0	5.3	4.9	12.2	11.6	3.3	350	4.1	4.3	2.55	64	26.0	81
3.4	4.4	.83	2.3	3.3	18.2	17.5	1.5	159	3.1	2.9	1.84	69	18.9	68
3.1	3.7	.5	1.75	3.7	16.4	15.5	1.25	132	3.2	2.2	1.76	71	13.5	57

Columns (1) and (2) represent the high and low values of the line pressure and (3) and (4) the mask or lung pressures as measured from the records. 1 cm on the record represented 3.1 cm H_2O for the line pressure and 1.67 cm H_2O for the lung pressures. Col. (5) is the duration of the cycle in seconds measured from the record. Col. (6) is 60 ÷ Col. (5). Col. (7) is the frequency as counted at the same line pressure with a stop watch. Col. (8) is Col. (4) - Col. (3). Col. (9) = 106 x Col. (8). Col. (10) is the total flow as measured from the gas meter in liters per minutes while Col. (11) is the same given by the product of Cols. (9) and (6). Col. (12) is the square root of Col. (1) and is used in plotting in Fig. 5. Col. (13) is the duration of inspiration in percent of the cycling time, Col. (5), as measured on the records. Col. (14) is Col. (3) x 100 ÷ Col. (2), and represents the minimum cut-off pressure in % of line pressure. Col. (15) is Col. (4) x 100 ÷ Col. (1) and represents the maximum cut-off pressure in % of line pressure. There is probably some error at the lower pressure due to zero shift.

Figure 5
Ordinates should be labelled "Cycle time in Seconds."

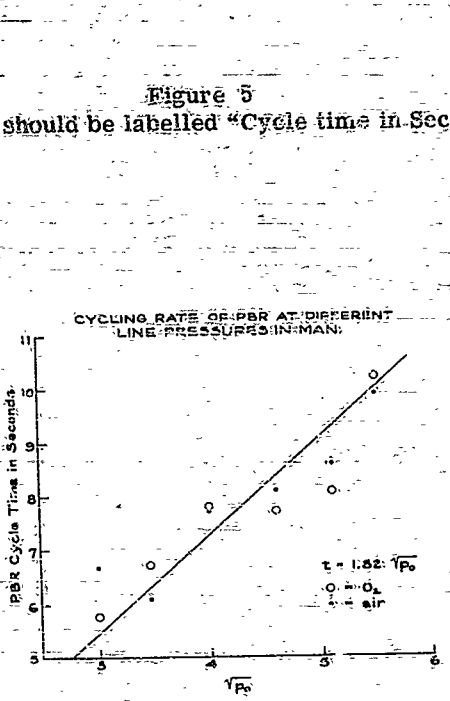

Figure 6

B. Experimental

The theoretical equation has been tested first on a simulated lung. Such a lung can be most easily and reliably obtained by the use of a large rigid container of about 100 liter capacity. We have used for this purpose an ordinary kitchen boiler. Since the atmospheric pressure is about 1000 cm. H_2O an increase of 1 cm. H_2O pressure is obtained when 100 cc. of air is forced into the "lung" and this is close to the slope of the relaxation pressure curve of the average human chest. For our "lung", A had a value of 9.4 in the equation $p = AQ$ where p is in cm. H_2O and Q is the volume of air forced into the lung in liters.

The PBR was connected to the 110 liter simulated "lung" on one side and through a gas meter to a line pressure of pure oxygen controlled by a Pioneer demand regulator. The "lung" pressure and the line pressure were recorded by optical manometers recording on a moving-paper camera. Frequency of cycling and liters of flow per minute were recorded both on the camera and by observation of the gas meter and a stop watch. Line pressure fell slightly during inspiration. The line pressure was varied over as wide a range as possible. The data are given in Table 1.

In Fig. 5 the duration of the cycle in seconds is plotted against the square root of the line pressure. For the latter we used the lowest reading during the cycle because this was maintained throughout most of inspiration. The results fall around a straight line through the origin in accordance with the equation derived above. The equation of this line is

$$t = 1.9\sqrt{p_o}$$

Now according to the theory

$$t(\text{inspiration}) = \frac{.86\sqrt{p_o}}{Ak}$$

where A = 9.4 and $k = \frac{3.6}{60}$ when Q is in liters per sec. for oxygen.

$$\text{then } t = \frac{.86 \times 60\sqrt{p_o}}{9.4 \times 3.6 \times .64} = 2.33\sqrt{p_o} \text{ seconds}$$

This theoretical constant 2.33 is somewhat larger than the observed value of 1.9 possibly due to the lack of precision in the measurements. The form of the equation however is the same.

When the PBR is used on man there are more opportunities for variations in the assumed conditions but it is nevertheless of interest to check this equation further by data from Motley et al. as plotted in Fig. 6. The straight line would pass through the origin if the chart were extended and it has a slope of 1.82 agreeing closely with value of 1.9 obtained with the simulated lung. The two instruments were not of course identical so that the agreement is of no great significance.

6. RELATION BETWEEN TOTAL VENTILATION AND LINE PRESSURE

A. Theoretical

The total ventilation (V) in liters per minute is given by the equation

$$V = Tf \quad \text{(tidal volume x frequency)}$$

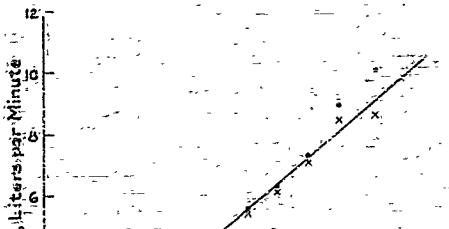

Figure 7

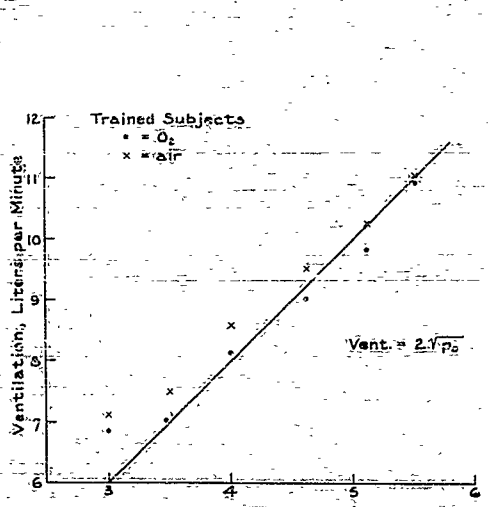

Figure 8
Data of Motley et al.

$T = \frac{\Delta p}{A}$ and $\Delta p = a\, p_o$ where a is a constant

Then $T = \frac{a\, p_o}{A}$

The cycle time in minutes t is given by

$$t = \frac{.86\sqrt{p_o}}{.64\ AK} = \frac{\sqrt{p_o}}{2.6A} \quad \text{when } k = 3.6$$

Since $f = \frac{1}{t}$ and $a = 0.56 = .81 - .25$

$$Tf = V = \frac{.56\ p_o}{A} \times \frac{2.6A}{\sqrt{p_o}} = 1.44\sqrt{p_o} \qquad \text{(equation 5)}$$

and A cancels out.

B. Experimental

From the data of Table 1 a plot is made of the ventilation in liters per minute against the square root of the line pressure. (Fig. 7). The points lie along a straight through the origin the equation of which is $V = 1.72\sqrt{p_o}$.

The experiment confirms therefore the form of the theoretical equation. The value of the constant is too large probably because our instrument shows some outflow leakage during inspiration.

C. Data from human subjects

It is only in completely passive ventilation of the PBR in man that it could be expected that this ventilation equation would be obeyed. When the pressure falls too low and ventilation becomes inadequate the subject will tend to lead the machine so that the mean pressure gradient is higher both on inflow and outflow. The data of Motley for trained subjects using O_2 and air are plotted in Fig. 8. Except for the expected divergence at low pressures the figures are reasonably well represented again by a straight line through the origin obeying the equation $V = 2\sqrt{p_o}$.

7. THE EFFECT OF LUNG VOLUME AND ELASTICITY ON THE PBR

An increase in lung volume has the same effect upon the cycling frequency and the ventilation as an increase in extensibility of the lung and chest. Both effects can be studies by varying the volume of a simulated lung in a rigid container. The only mechanical factor omitted in such a simulated lung is the viscous loss in the air and in the tissues when they are deformed. Using this artificial system then the problem is to determine the effect of different "lung" volumes. Records were accordingly taken of pressure changes in line and lung while the PBR was cycling at a constant line pressure setting but with lung volumes varying from 110 liters to 900 cc (including tubes).

A. Theoretical

In deriving equation 5 for the ventilation it was shown that the quantity A cancels out in numerator and denominator so that the final equation is $V = K\sqrt{p_o}$

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TABLE 2

Effect of "Lung Volume" on the PBR

(1) Vol. in "lung"	(2) line in cm. min	(3) pressure H_2O max	(4) lung in cm. min	(5) pressure H_2O max	(6) $\frac{p}{Po} \times 100$ min	(7) $\frac{p}{P_0} \times 100$ max	(8) Total ventilation lit/min	(9) Frequency per min	(10) Tidal vol. cc	(11) Time for inspiration in % of cycle	(12) Calcd lung vol liters
110	15.6	19.6	3.2	12.8	16.3	82	7.2	7.05	1020	63	106
20	17.0	19.8	3.8	12.3	19.2	72	7.3	39.5	183	64	21.5
9	17.2	19.6	3.8	12.8	19.3	74	7.8	80	98	65	10.9
0.9	13.2	20.5	10	12.8	49	97	9.4	480	19.8	3	0.7

Col. (1) is the measured volume of the lung and tubes. Cols. (2) and (3) are the maximum and minimum line pressures measured on the record being 3.1 x the cm on the record. Cols. (4) and (5) are the pressures recorded from near the "lung" being 1.67 x the cm on the record. Col. (6) is Col. (4) divided by Col. (3) x 100 because (3) was the line pressure at the time when expiration terminated. Col. (7) is Col. (5) divided by Col. (2) times 100 because Col. (2) was the line pressure when inspiration was terminated. Col. (8) is the minute volume of the ventilation in liters measured from marks recorded on the film at the beginning and end of one revolution of the gas meter. Col. (9) is the frequency in cycles per min. Col. (10) is Col. (8) divided by Col. (9). Col. (11) is the duration of inspiration in percent of the length of the cycle (not measureable from the record at the smallest volume). Col. (12) is Col. (10) divided by Col. (5) minus Col. (4). This is because $p = \frac{T}{V} \times B$ where B is the barometric pressure in cm H_2O = 1000 (if B = 740 mm Hg). Hence the volume of the lung

$V = \frac{1000T}{\Delta p}$ where T is in liters.

Since A is the only quantity which varies with the lung volume it may be concluded that the total ventilation in liters per minute is independent of the size or elasticity of the lung.* If the lung is very small or very stiff it fills up to the critical pressure rapidly so that the frequency is increased in proportion to the decrease in tidal volume. If a constant fraction of the time is spent in inspiration and if the mean pressure gradient during this time is constant, the total inflow should be the same regardless of frequency.

B. Experimental

The results are listed in Table 2. The ventilation (Colume 8) is nearly constant, as demanded by the theory, except at the smallest volume where the rate was 480 and some leakage may well have occurred during expiration. At the other volumes the gas meter always indicated no flow at all into the mask during expiration. The general reliability of the measurements is indicated by the agreement between the calculated and observed volumes of the lung in the first and last columns.

The critical cycling pressures were 16 to 19% of the line pressure at expiration and 72 - 82% at inspiration. The values at the highest frequency are in error presumably because the pressures were recorded near the lung rather than near the mask. A 4 ft. length of 3/4" rubber tubing separated these 2 points which is probably enough for the existence of an appreciable pressure difference at a rate of cycling of 480 per minute but would have no significant effect, we believe, at lower rates.

8. SAFE FREQUENCIES FOR PASSIVE VENTILATION ON THE PBR

One of the advantages of the PBR is that it is always possible to tell from the frequency of cycling whether or not the ventilation is adequate. The problem is presented therefore of calculating the frequencies at different line pressures which are consistent with adequate ventilation of the alveoli. As an adequate ventilation it may be assumed that 5 liters per minute, exclusive of the dead space ventilation, is required for a normal pCO_2 in the alveoli.

It has been demonstrated that the ventilation is given by the equation $V = 2\sqrt{p_o}$. This minute volume is furthermore independent of the size and elasticity of the lung. Even if the glottis is closed so that the PBR chatters, the total flow of oxygen through the valve will remain approximately the same as if the instrument were cycling properly. The difference is that at high frequencies all or a large fraction of the moving air ventilates only the dead space because the tidal volumes are too small to reach the alveoli.

The aleolar ventilation, Valv. with an assumed dead space (including the mask) of .3 liters is given by the equation.

$$Valv. = 2\sqrt{p_o} - 0.3\,f$$

The maximum frequency, f, consistent with Valv = 5 liters is therefore

$$f\,max = \frac{2\sqrt{p_o} - 5}{0.3} \qquad \text{(equation 6)}$$

* The total ventilation would vary with viscosity and turbulence in the air stream. The formula gives therefore a maximum value since it neglects these factors.

Values of f max calculated from this equation are plotted in Fig. 9. Ventilation rates greater than those indicated by this graph would be expected to result in inadequate ventilation regardless of the cause of the high rate. The position of the curve will vary somewhat with the size of the dead space and the size of the inflow and outflow openings in the instrument. If the individual is "leading the machine" in an effort to increase his tidal volume and still has a high frequency this curve would not apply.

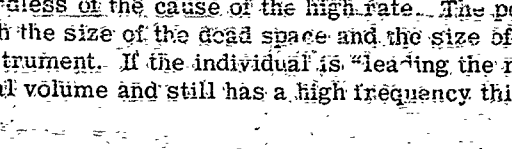

Figure 9

Maximum and minimum frequencies of cycling which are consistent with adequate ventilation of the alveoli at different line pressure.

For a normal chest where A has a value of about 10 ($p = \frac{T}{10}$) there is also a minimum frequency below which it is not possible to go without sacrificing alveolar ventilation. For each line pressure (p_o) there is a corresponding change in lung pressure (p) such that $p = ap_o$ where a (in our instrument) is 0.56. With such a pressure change the tidal volume (T) should be $T = \frac{.56\ p_o}{10}$ and the alveolar ventilation, Valv, will be

$$Valv = (.056\ p_o - 0.3)f$$

To obtain an alveolar ventilation of 5 liters per minute the frequency must be at least

$$f\ min = \frac{5}{.056\ p_o - 0.3} \qquad \text{(equation 7)}$$

Values calculated from this equation have also been plotted in Fig. 9.

The shaded area between these 2 curves represents therefore the area of adequate passive alveolar ventilation. It is interesting to note that the frequencies actually observed by Motley using trained subjects on O_2 (see curve Fig. 9) lie within this shaded area with the exception of the 2 points at the lowest pressures where the ventilation might well have been inadequate unless the subject was

lowering the rigidity of his chest (lowering his f min) or increasing the inflow pressure gradient (raising f max) by active efforts. In our experience this is what happens on the PBR at low pressures.

9. FREQUENCY OF CYCLING AT ALTITUDE

The duration of inspiration according to equation 4 is given by the expression

$$t = \frac{.86\sqrt{p_o}}{A\,k}$$

and the frequency is the reciprocal of $\frac{t}{.64}$ or

$$f = \frac{.54\,Ak}{.86\sqrt{p_o}} \quad \text{or} \quad \frac{7k}{\sqrt{p_o}}$$

According to equation 1, k varies with altitude according to the expression $k = \sqrt{\frac{96}{B}}$ where B is the barometric pressure in mm Hg. Hence the frequency as a function is

$$f = \frac{672}{\sqrt{p_o B}} \quad \text{or the cycle time} = \frac{\sqrt{p_o B}}{672} \text{ minutes or } .089\sqrt{p_o B} \text{ seconds.}$$

As the altitude increases therefore the frequency should also increase.

This theoretical conclusion is borne out by experiment as shown in Table 3. In these experiments the line pressure was always 30 cm H_2O. Three subjects using the PBR made simulated ascents to 25 and 34 thousand feet. Total ventilation and frequency were recorded at ground level before and after the flight as well as at altitude. Subject A.C. apparently overventilated at ground level before the flight but with this exception the frequency and the ventilation were higher at altitude. All three subjects had a tendency to lead the machine at ground level because of the feeling that the air supply was not adequate. At altitude breathing was easy and comfortable.

A more precise confirmation of this theory is given by date of Brown on the cycling rate of the PBR when used on dogs resuscitated after cessation of respiration at 38000 feet and then brought down to ground level by stages. In Figs. 10 and 11 the cycle times for 2 of these dogs are plotted against the square root of the barometric pressure. The data fall along a straight line through the origin.

The slope of this line cannot be compared directly with the theoretical slope calculated for man on account of the smaller size of the lung and the fact that 3 of the 6 inflow holes in the PBR were occluded for use in dogs. Considering these factors the constants are reasonable in magnitude.

10. A STUDY OF THE FACTORS WHICH CAUSE THE PBR TO CHATTER. FLOW THROUGH ORIFICES INTRODUCED BETWEEN THE MASK AND THE SIMULATED LUNG

For orifices we used round holes drilled in thin (0.3mm) metallic bottle caps which fitted into the rubber tubing between the mask and the "lung." The nature of the flow through such holes is well known but we made some measurements in order to obtain the value of k for each orifice in the equation Flow = $k\sqrt{p_o}$. The results obtained with 4 different orifices are shown in Fig. 12. The same data

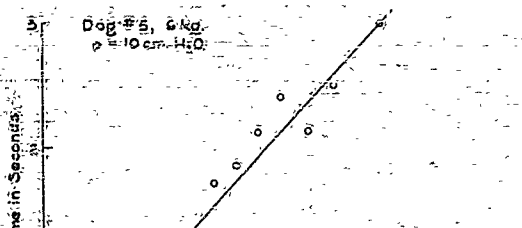

Figure 10

Data of B. R. Brown

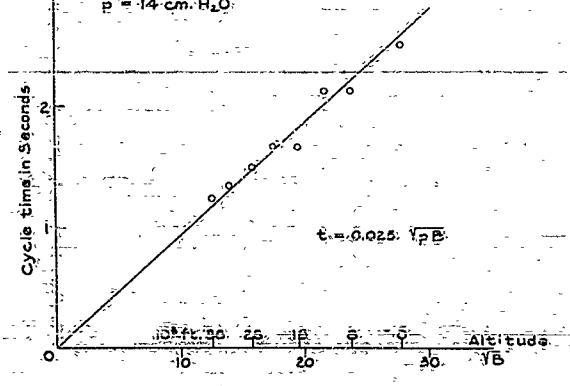

Figure 11

Data of Brown

TABLE 3

The PBR at Altitude

Subject	Altitude	Line Pressure	Mask Pressure	Frequency	Mean Tidal	Total Vent	Est. Alv. Vent *	Foot note
	Feet	cm H_2O			cc	Liters/min		
A.B.O.	0	23-30	4-18	4.5	1631	7.34	6.45	(1)
A.B.O.	25,000	22-29	3-18	10.3	1070	11.00	8.96	(2)
"	34,000	22-30	3-18	12.4	920	11.40	8.92	(2)
"	0	22-31	3-19	7.9	1230	9.70	8.12	(3)
A.C.	0	22-31	3-20	13.5	860	11.60	8.90	(4)
	25,000	22-31	3-20	9.8	1065	10.45	8.48	(2)
	34,000	22-31	3-19	11.7	916	10.71	8.37	(2)
	0	22-31	3-20	7.8	1130	8.80	7.25	(4)
W.O.F.	0	22-31	-1-22	6.0	1122	6.74	5.54	(1)
	25,000	22-31	3-21	9.2	1360	12.70	10.85	(2)
	34,000	22-31	3-21	12.0	939	11.30	8.88	(2)
	0	22-31	-1-22	7.6	1082	8.52	6.70	(4)

* Assume dead space = 200 cc
(1) Lead machine at start of inspiration
(2) No desire to lead machine
(3) Did not lead machine, altho difficult not to
(4) Lead machine occasionally

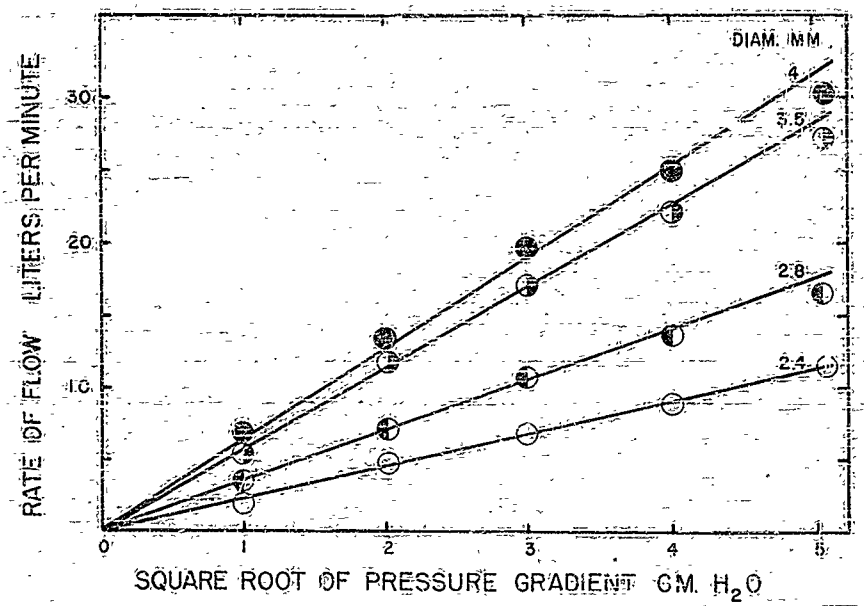

Figure 12

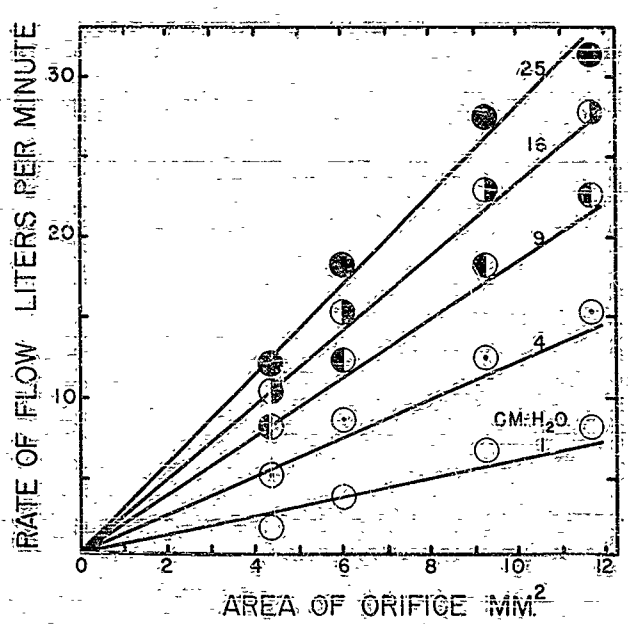

Figure 13

plotted against the cross sectional area of the orifice shows that with a constant pressure gradient the flow is directly proportional to this area, Fig. 13. In general it was found that when the k for the orifice in use was smaller than the k for inflow into the mask the PBR was near the chatter threshold. We are unable to predict on theoretical grounds the exact chatter point because the equations involved became too difficult. The data of Table 4 are of interest in this connection and they show that there is no true cycling until the k for the orifice is 10.6 which is greater than either the inflow constant 7.3 or the outflow constant 10.0.

TABLE 4

Effect of Orifice Resistances Between PBR and 20 Liter Simulated Lung

Diam. of orifice mm.	Area of orifice mm^2	Flow $\frac{}{\sqrt{p}} = k$	Remarks	Lung Pressure p_1/p_o
2.83	6.3	2.3	no true cycling*	.40
3.0	7.1	3.5	" " "	.40
3.3	8.5	5.6	" " "	.39
4.0	12.6	6.3	cycles above 6 cm.	—

* Above a certain pressure of 10-20 cm., the valve seems to catch at intervals and cause a brief up-swing of line pressure and lung pressure. This action seems to differ from true cycling. Below this point the valve is in a mid position so that air flows both in and out continuously. The last column gives the lung pressure, p_1, as a fraction of the line pressure, p_o.

When the PBR chatters there is no ventilation of the lungs. When it is not truly chattering but merely cycling very rapidly the alveolar ventilation may also be too small. This can be obviated by increasing the extensibility of the mask, or to some extent by raising the line pressure, or by reducing the value of k_i by occluding one or more of the 6 inflow openings. The pressure then rises slowly enough in the mask so that the flow into the lungs through a narrowed orifice can be increased. The smaller the orifice the smaller the ratio of p in the lung to p in the mask. When the orifice is so small as to cause chattering some ventilation of the alveoli can nevertheless be obtained manually if the line pressure is alternately turned off and on. Since however at the chatter point the lung pressure only builds up to about 0.4 of the line pressure and since this pressure rises and falls very slowly because of the high resistance, the amount of alveolar ventilation which can be obtained in this way is not large enough to be of much practical use. It would seem better to take drastic measures to clear the air way rather than to continue the struggle against a chattering valve.

11. RELATIVE DURATION OF INSPIRATION

It has been shown in section 1 that outflow in the PBR is 1.7 times as rapid as inflow. Outflow might therefore be expected to be correspondingly short and inspiration should occupy 17/27 or 63% of the cycle in passive breathing.

The duration of inspiration measured on the same instrument on a simulated lung averaged 66%. Motley reports average values of 43% and records kindly sent to us by Dr. Boothby have indicated a duration of 47%. These low values may indicate an acceleration of inflow by active suction by the subjects unless they were obtained on instruments which were very different from those available here. This value may also be modified to some extent by the small leak during inspiration which we were not able to avoid.

SUMMARY

1. Inflow and outflow through the PBR are both turbulent in nature and proportional to the square root of the pressure gradient. Out flow is faster than inflow so that expiration time should be shorter than inspiration time in passive breathing.

2. The frequency of cycling decreases as the line pressure increases. The duration of the cycle is directly proportional to the square root of the line pressure.

3. The total ventilation in liters per minute is equal to $k\sqrt{p_o}$ where p_o is the line pressure in cm H_2O and it is nearly independent of the volume or elasticity of the lung. The value of k is about 2.0.

4. A chart is prepared to show the maximum and minimum frequencies which are consistent with adequate alveolar ventilation at different line pressures. At line pressures of 20 and 30 cm the frequency should not exceed 13 and 20 per minute respectively for an alveolar ventilation of 5 liters per minute and a dead space of 300 cc.

5. The cycle time at altitude decreases (frequency increases) in direct proportion to the square root of the barometric pressure (at constant line pressure).

6. True cycling is not obtained if the orifice between the PBR and a simulated lung is smaller than 4 mm in diameter. In general there is no cycling if the flow constant $\left(\frac{\text{lit/min}}{\sqrt{p}}\right)$ of the orifice is less than the inflow and outflow constants of the PBR.

7. The lung pressure when the PBR "chatters" is about 40% of the line pressure and remains constant.

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SUMMARY OF INVESTIGATIONS ON THE BURNS PNEUMATIC BALANCE RESUSCITATOR

by

Wallace O. Fenn, Rochester, New York

Submitted to
Aero Medical Laboratory, Wright Field
September 30, 1945

I. Mechanical

The mechanical behaviour of the PBR has been described by Burns (1944) and by Fenn, Otis, and Rahn (1945). The main features have been confirmed by all who have worked with it and may conveniently be summarized in a few simple equations or the corresponding charts. The exact numerical constants in the various equations depend upon the particular instrument which is used and to some extent upon the particular subject. It is recommended that the numerical values given below be checked on a sufficient number of instruments and subjects so that a reliable mean figure with its standard deviation can be supplied.

1. The total ventilation (at (20-25° C, ambient pressure, dry) obtained with the PBR in liters per minute at ground level is equal to $2\sqrt{p}$ where p is the line pressure in cm. H_2O (The constant 2 varies from 1.7 to 2.5 in different reports.) The value of the constant depends upon the flow characteristics of the instrument and is largely independent of the size or elasticity of the lungs of the subject or the frequency of cycling. When p = 25 cm H_2O the ventilation equals 2 x 5 = 10 l/min.

2. The ventilation varies inversely with the square root of the barometric pressure so that the amount of completely passive ventilation expected at altitude is equal to $2\ p\sqrt{\frac{760}{B}}$ x = $55\sqrt{p}$/B. Thus at 25,000 feet the ventilation would be 16.5 lit/min. (The correction to body temperature, saturated, is greater at altitude than at ground level because of the relatively greater fraction of the pressure due to water vapor.)

3. At ground level the frequency varies inversely as the square root of the line pressure is equal approximately to $\frac{33}{\sqrt{p}}$ cycles per minute in completely passive breathing. The numerical value of the constant increases with increasing rigidity of the thorax.

4. At altitude the frequency is higher than at ground level because of the lower density of the air and is equal to $\frac{910}{\sqrt{pB}}$ cycles per min where the line pressure, p is the cm H_2O and the barometric pressure, B, is in mm. Hg. The exact magnitude of the constant depends upon both the subject and the instrument.

5. The instrument fails to cycle or chatters if the airway is narrowed to less than 1/8 inch (Burns) in diameter.

6. The instrument has proved to be reliable in practice and has caused little trouble by failing to operate for any reason.

7. The PBR faithfully follows the breathing pattern of the subject without difficulty or discomfort.

8. If the subject requires more ventilation than the instrument can supply this is supplied by a relief valve in the mask which permits ambient air to enter when the mask pressure falls below zero. This never happens in normal cycling.

9. About half the cycle is occupied in inspiration the exact fraction being dependent upon the relative inflow and outflow resistances for purely passive ventilation. To some extent the inspiration time can be varied by the activities of the subject.

10. The mean mask pressure averages only 42% of the line pressure (Motley et al).

II. Physiological

Rather extensive investigations of the physiological aspects of the PBR have been carried out in the past year in 8 different laboratories and there seems to be general agreement as to the results.

1. Adequacy of ventilation in conscious subjects. At low line pressures all subjects feel air hunger but at a sufficient pressure (above 12 cm) or at a sufficient altitude the breathing is easy and the ventilation adequate. If the ventilation is expressed as kvp then k as calculated from data of different investigators with different PBR models varies between 1.7 and 2.5.

When the ventilation is inadequate it can be increased to a limited extent if the subject "leads the machine" actively thus increasing the mean pressure gradient.

In unconscious subjects the metabolic demand for air is not essentially different from that in conscious subjects. Judging by the general clinical condition of the patient the ventilation supplied by the PBR is also adequate in this case.

2. Hyperventilation. While it is next to impossible to hypoventilate a conscious subject because of the efforts which he instinctively puts up in his own defense, it is easy to hyperventilate because of the effects of lowered CO_2 tension remains unnoticed and are reflexly opposed to a small extent only. The acapnia produced by the PBR is not however of importance except perhaps to a slight degree at high altitudes.

Measurements of alveolar CO_2 tension and CO_2 loss from the body have been made by Olson at the Mayo Aero Medical Laboratory, (1944), Rahn et al (1945), Berg (1945), and Motley (1945). Berg found a loss of CO_2 at pressures about 17 cm. but not at 11 cm. The lowest alveolar CO_2 tensions found by Rahn et al at 18-20 cm H_2O were 29-30 mm (except for one subject at 27). Olson (1944) reported on the average no change in alveolar CO_2 tension. Motley found no change of ventilation

at sea level in trained subjects but a 51.7% increase in untrained subjects. The increases were greater at 25,000 feet in both types of subjects but even here the lowest alveolar pCO_2 reported was 25 mm Hg. The lowest arterial $p\,CO_2$ reported at sea level was 27 mm in one patient and no value lower than 29 mm in 8 other patients. It must be concluded that at the higher pressure settings, particularly in untrained subjects, and particularly at altitudes there is some tendency to acapnia on the PBR but the degree of acapnia is in no case sufficient to cause any significant symptoms.

3. Cardiac Output. At 22 cm of H_2O an average decrease of cardiac output of 27% was reported by Rahn et al by the ballistocardiographic technique. By the superior direct Fick technique Motley et al reported an average decrease of 22% at line pressures of 16-30 cm H_2O. The greater the pressure the greater the effect on cardiac output. This constitutes a definite reason against the use of high pressures in resuscitation. The pressures used should therefore be as small as is consistent with an adequate ventilation. In one case in circulatory shock reported by Motley the PBR caused no further reduction in cardiac output so this circulatory inhibition is not regarded as a serious objection to PBR resuscitation.

In formulating a recommendation concerning the most favorable pressure to use it is necessary to balance the danger of curtailment of the circulation against the possibility of an inadequate ventilation. Since the arterial blood pressure is not reduced by the PBR even though the cardiac output is diminished there is little reason to believe that the coronary or cerebral circulations are less well maintained than normal. Hence priority should be given to the maintenance of adequate ventilation in spite of possible effects upon the circulation which may not be of real importance.

4. Other circulatory effects. On the average the data reported by Motley show an increase of arterial systolic pressure of 10 mm for an average increase of mask pressure of 9 mm Hg. Evidently there is a peripheral vasoconstriction as in continuous pressure breathing which maintains the arterial pressure level even though the cardiac output is diminished.

The rise in peripheral venous pressure is 38% of the mean mask pressure (Rahn et al) and the rise in right auricular or central venous pressure is on the average 47% (Motley). This represents a compensation for the elevated intrathoracic pressure and prevents the cardiac output from falling still lower.

In dogs under anesthesia it has been reported by Ivy (3/14/45) and by Davis and Orth (4/23/45) that the application of the PBR causes an initial fall in arterial pressure which soon returns to normal. On removing the PBR the reverse changes occur. Gradual elevation of the pulmonary pressure caused a gradual decline of mean arterial pressure in anesthetized dogs (Ivy) but this apparently did not occur in unanesthetized men (Motley).

5. Safe frequency of cycling. In a discussion of the mechanical features of the PBR it has been shown that the frequency increases because of (1) diminished airway, (2) increased rigidity or decreased volume of the lung and thorax, (3) decreased

barometric pressure or density of gas (helium) or decreased line pressure. The most important of these for practical purposes is the blockage of the airway. When this occurs the alveolar ventilation decreases, the dead space ventilation increases, but the total ventilation remains largely unchanged. Knowing the volume of the dead space, d, the dead-space ventilation, df, can be calculated and subtracted from the total ventilation. If the remainder is less than about 4 or 5 liters it may be concluded that the blockage of the airway must somehow be relieved or the total ventilation increased by the use of more pressure if asphyxia and cyanosis is to be avoided. The following table will indicate the approximate safe frequencies at different pressures (cm H_2O).

Safe frequencies at various line pressures

Ventilation alveolar l/min	total l/min	dead space cc.	Cycles per minute 10	20	30	cm H_2O
5	$2\sqrt{p}$	200	6	20	30	
5	$2\sqrt{p}$	300	4	13	20	
4	$2.5\sqrt{p}$	200	20	36	48	
4	$2.5\sqrt{p}$	300	13	24	32	

The lowest dead space which can be assumed (with the mask) is 200 cc as reported by Rahn et al. Motley et al however give 180 cc as the volume of the A-13 mask making a total dead space of about 300 cc. The highest total ventilation that can be assumed from published reports is $2.5\sqrt{p}$ and an alveolar ventilation of 4 liters per minute is just sufficient to give a normal alveolar p CO_2 of 38 mm Hg if the rate of oxygen consumption is 220 cc/min which is a low figure for a normal man. The highest rates which could reasonably be permitted are therefore those which are underlined in the table.

Since the dead space can not change much in anoxia these figures are valid whatever the reason for the increase in frequency. If these rates are much exceeded even at the lighter pressure then strenuous efforts should be made to open the airway. This is not a disadvantage of the PBR but should rather be regarded as one of its great advantages because it constitutes a simple and reliable index of the amount of ventilation actually being accomplished. A high rate or a chatter of the valve indicates that fluid is accumulating in the trachea or bronchioles or that the glottis is occluded. In the Drinker respirator on the other hand the cycling apparatus is entirely independent of the response of the subject and there is no ready index of the degree of ventilation which is actually accomplished.

An excessively slow rate of 3 per min may be caused by leakage of the mask. This will result in inadequate alveolar ventilation even though the elasticity of the chest and lungs remain perfectly normal. If the chest becomes abnormally stiff the minimum safe frequency is higher than 3 per minute. The object should be therefore to make the rate as high as possible without exceeding the safe limits stated above. A high line pressure (above say 20 cm, or above 12 cm according to Motley) should be avoided on account of the resulting decrease in cardiac output.

6. Oxygen consumption and CO_2 output. Motley et al reported a decrease in the rate of oxygen consumption of 2% but felt doubtful whether this was outside the limits of the experimental error. In 9 experiments reported by Olson at the Mayo Laboratory there was an average decrease of 1.5% but this resulted from 2 increases, 3 decreases, and 4 experiments without appreciable change so that the statistical significance is doubtful. Berg reported a 6.2% decrease in oxygen consumption with PBR No. 1 and No. 2 but a slight rise with model No. 3. Special attention should be called to the danger of estimating the rate of oxygen consumption from the volume of O_2 content of expired air because of the danger of losing an appreciable volume by leakage out of the mask. Motley avoided this error by using inspired volumes in his calculations thereby obtaining much smaller decreases in rate of oxygen consumption. In any event these results do not suggest any important physiological change in metabolism due to the PBR.

Whenever the ventilation is increased by the PBR the CO_2 output is of course likewise increased but when this is avoided the rates of CO_2 output do not change more than the rates of O_2 consumption.

7. Damage to the lungs. Experiments were reported by Davis and Orth (5/15/45) on 44 dogs, 6 of which served as controls and the remainder were "resuscitated" under anesthesia for 6 hours by various methods including the PBR on 6 of the animals. Abnormalities were found in all the dogs but they were no greater under the PBR or any other form of artificial respiration than in the control animals. Ivy came to a similar conclusion. At least 2 patients have recovered without difficulty from a similar period on the PBR. The pressure applied by the PBR is therefore harmless to say the least.

III. Clinical Cases

The PBR has been used on some 30 or more normal conscious subjects and on 70 patients according to records now available. Of the latter, 33 (Olson 4/26/45) were recovering from an anesthetic and were breathing spontaneously. The others were mostly unconscious, apneic or moribund. Almost without exception the reports were entirely satisfactory so far as the operation of the valve was concerned.

Of 12 cases reported by Dr. J. A. Luetscher Jr. at Johns Hopkins 6 were moribund and in 3 the rate was excessively rapid as if the airway were obstructed. Since the tidal volumes were read from the expired air there is also a possibility that the same air was lost by leakage under the mask. In later reports satisfactory operation was observed in 5 patients one of whom breathed through the PBR successfully for 4 days!

Dr. Orth at Wisconsin reported successful use of the PBR on 7 patients, 4 of them for 6, 9, 13, and 18 hours respectively. All of these were apneic or breathing irregularly when the PBR was applied. No difficulties were encountered.

Major Olson at the Mayo Clinic used the PBR on 3 cases in addition to the 33 post anesthetic patients. Two of these cases were apneic and the third used the PBR for 72 hours intermittently for the relief of asthma. In these cases also the operation was satisfactory.

Motley and others at Bellevue Hospital have used the PBR on 10 patients in deep coma and 2 in semi-coma. One of the former continued for 19 hours. In all these 12 cases no trouble with the airway was observed except possibly one case where it could be remedied by hyperextension of the head and raising the jaw. Chattering of the valve was also observed for a time in one case of Cheyne-Stokes respiration during the periods of apnea. In cases with moist rales the application of the PBR cleared up this condition after 45-60 minutes but did not improve the circulatory failure.

In one fatal case of infantile paralysis observed by the writer the PBR was used at intervals for about 2 days. The only difficulty encountered was the frequent occlusion of the airway due to fluid in the trachea. This was always indicated by the chattering of the PBR. After aspiration of the fluid through a naso-tracheal tube the valve cycled properly.

Reports are available of the application of the PBR to 15 persons shortly after death. Dr. Lundy at the Mayo Clinic reported 2 cases, only one of which could be ventilated. Ivy at Northwestern University reported in 4 cases that the PBR cycled too rapidly or chattered while the E and J and the G-E pneumolator ventilated successfully. Burns at Wright Field tried these instruments on a simulated lung however and found the PBR more "tolerant" of an artificial constriction in the airway than the G-E pneumolator. The writer found it more tolerant than the Emerson resuscitator.

Motley tried the PBR on 9 fresh cadavers and found that chattering usually results unless the head is hyperextended. An artificial airway was of no assistance and the tongue caused no trouble. As rigor mortis developed the rate increased. One case was continued for 8 hours without failure of the ventilation.

In addition to the work on human subjects the PBR has been used successfully by several investigators for the resuscitation of dogs after anoxia. [Wulff, 2/10/45 Brown, 1945, Ivy, Capt. Swan, (Wright Field) Davis and Orth, 3/10/45, and others]. For use on animals it is desirable to close some of the inflow openings to prevent excessively rapid cycling.

Conclusion. From these reports it can be concluded that; (1) the PBR is effective in providing artificial respiration to patients and fails only under conditions of airway blockage when any resuscitator will function poorly. (2) The only practical difficulty is that of avoiding mask leakage. (3) The rapid cycling of the PBR when the airway is obstructed is a valuable danger signal. (4) The PBR promises to be useful in medicine because of its portability and simplicity.

IV. Comments

After the cessation of respiration recovery with any form of artificial respiration is possible for only a few seconds or minutes. The few cases which have recovered after drowning only after prolonged application of artificial respiration are exceptional. They perhaps indicate that in a few persons the relative sensitivity of the respiratory center is abnormally great so that this part recovers very slowly

although other parts of the nervous system and the circulatory system in general recover more promptly. In any event it is certain that time is more important than technique when an asphyxiated victim is discovered. It is more important therefore to apply some or any sort of manual resuscitation at once than to run after a mechanical gadget. Later if it is possible to obtain a resuscitator it can be applied to good advantage. A resuscitator is better than a manual method if it can be used with as little delay. In recommending the use of a mechanical resuscitator in the Air Force this proviso is emphasized.

There are certain disadvantages to the PBR which might be mentioned. At temperatures below 0°C the valve will freeze in a few breaths but if the valve and mask are kept warm before application they will function properly for as long as 10 minutes (Burns).

The valve cycles according to the pressure limits attained in the mask rather than the pressures in the lungs so that it is possible for it to ventilate the mask without adequate ventilation of the lungs. In practice this is not as serious a matter as it first appears because the high rate of cycling is an obvious index of this "mask-only" ventilation and permits remedial measures to be undertaken.

Due to the many concealed recesses in the PBR it is difficult to clean and sterilize it adequately after use on an infectious case. In military operations of course this is not a particularly pertinent problem and it can be accomplished with suitable directions. In one case the membrane was observed to stick temporarily due to inadequate cleaning after the patient vomited into the mask.

Resuscitators which include a negative pressure phase have an advantage over a positive pressure apparatus like the PBR in that they can utilize a wider pressure range without exceeding safe pressure limits on either the negative or the positive side. It has been argued, to be sure, that negative pressure is harmful because of the danger of pulmonary edema, but the evidence of any actual harm from limited negative pressures as used in resuscitation in modern machines in alternation with positive pressure is not impressive or convincing. It can however be argued that negative pressure is not necessary and the success of the PBR in recent trials supports this view.

While the PBR is durable it will be necessary to replace the rubber membranes perhaps once a year to ensure reliable operation. This requires some skill from an inexperienced man but can be done fairly quickly after an initial attempt.

According to Motley the chief difficulty in using the PBR is its dependence for normal cycling upon a good mask fit. Present masks have been designed to fit the faces of young military personnel fairly well but the smaller faces of women and sunken faces of old men may require new mask models if the PBR comes into extensive clinical use. (Motley).

A survey of the field of anoxic resuscitation indicates that many questions still remain to be answered. It is unnecessary to enumerate these questions here because they cannot change in any significant way the nature of the emergency treatment

which is required. To save a victim in respiratory distress some air or oxygen must be forced into the lungs as expeditiously as possible. First in importance is the speed and promptness with which this is done. Second in importance is the effectiveness with which it is done. After these items are cared for attention might be directed to other items which might affect the rate of recovery such as the biochemical changes in the blood and tissues, the anoxia thresholds in different parts of the nervous system, the rate of CO_2, enzymic and hormonal changes in the blood, physiological contractions of the airway etc.

As a technique for artificial respiration the PBR can be highly recommended on the basis of the extensive trials to which it has already been subjected. It is the most compact and portable automatic instrument available and has the minimum of moving parts. It has proved to be dependable in operation. Its success is dependent upon the patency of the airway but this is equally true of any method of artificial respiration including manual methods.

Most occlusions of the airway are due to relaxation of muscles around the glottis and can be obviated by pulling the jaw forward and upward and hyperextending the head. Obliteration of the airway by an actual spasm of the vocal cords seems to be a rare occurrence resulting only from the presence of foreign bodies or irritating fluids in the larynx. Laryngeal spasms and occlusion by accumulation of mucous or fluids in the trachea and bronchioles are both situations which require an endotracheal tube for treatment and can hardly be carried out successfully in the field. A pharyngeal airway is sufficiently easy to use so that it should be available as a last resort but it is not likely to be needed if the head and jaw are properly positioned and if this procedure fails the airway is not likely to be of much avail even if it is used, because the block is probably somewhere below the glottis.

Field tests of the PBR have been made by the navy in a PBY-2R and an R4D-6 modified for transport of wounded and they have shown that the PBR can be conveniently handled in planes at low altitude. (See N.M.R.I. Report.)

The direction for applying artificial respiration should be

1. Apply immediately any sort of manual resuscitation that the position and location of the victim permits.

2. Obtain a PBR and apply it as quickly as possible without undue interference with the manual method in the process. Then discontinue manual efforts.

3. Count the frequency of cycling and if it is faster than 36 at a line pressure of 20 cm H_2O make an effort to slow it down by pulling the jaw forward and upward and extending the head.

4. If this fails try to introduce a pharyngeal airway.

V. Conclusions

1. The PBR is compact, portable, and mechanically reliable and has been kept in continuous operation for as long as 4 days.

2. The PBR has received extensive tests in some 30 conscious normal subjects, 33 anesthetized breathing patients, 37 other patients mostly apneic, and 15 cadavers and many dogs in 9 different laboratories and hospitals as well as field tests in naval planes.

3. The PBR delivers air or oxygen under intermittent positive pressure and the volumes, pressures and rates of cycling have been well worked out at ground level and altitude in the form of charts and simple equations.

4. A table is provided to indicate the safe frequencies of cycling at various line pressures. This serves as a valuable criterion of the successful functioning of the apparatus at any time.

5. The chief difficulties to be expected in the use of the PBR for resuscitation are common to any mask-applied method and are (a), the leakage of the mask and (b) obstruction of the airway.

6. In most cases the obstruction of the airway can be obviated by manipulation of the lower jaw and hyperextension of the head or the introduction of an oropharyngeal airway. Other causes of obstruction such as accumulation of fluid in the trachea are not likely to be encountered in aircraft.

7. The characteristic chattering of the PBR when the airway is blocked serves as a valuable indication of the need to remedy the occlusion of the airway.

8. The application of the PBR causes a reduction in cardiac output without a fall in the arterial pressure.

9. Pressures not exceeding 12 cm of water are therefore recommended but higher pressures up to at least 20 cm or even 30 cm can safely be advised if they are needed for adequate ventilation.

10. The mean mask pressure is only about 42% of the stated line pressure.

11. No appreciable pulmonary damage has been demonstrable in dogs after 6 hours on the PBR.

12. The PBR produces some hyperventilation in normal subjects at ground level and more at altitude but not enough to produce significant symptoms of acapnia.

13. No significant changes in the rate of oxygen consumption occur although there will be a loss of CO_2 from the body if hyperventilation occurs.

14. The resuscitator will operate satisfactorily at temperatures above 0°C and will operate for as long as 40 minutes at -5°C if previously warm or at lower temperatures indefinitely if electrically heated.

15. While the PBR is recommended for military use, personnel should be instructed in manual methods so that these can be applied immediately without wasting valuable seconds in procuring and fitting up a PBR. The PBR should then be applied as soon as possible thereafter.

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PERFORMANCE AS RELATED TO COMPOSITION OF ALVEOLAR AIR[1]

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In a previous report (Rahn et al., 1946) some effects of hyperventilation on performance test scores were described. In these experiments oxygen was breathed at a simulated altitude of 30,000 feet. The results could be related to changes in alveolar carbon dioxide tension alone, since the alveolar oxygen tension never fell below the normal ground level range

The experiments reported below constitute an attempt to relate performance to alveolar gas composition when both the oxygen and carbon dioxide tensions are varied simultaneously and when one or the other is varied singly.

METHODS. All experiments were conducted in our high altitude chamber. Alveolar gas tensions were varied by 1, hyperventilation with the aid of the G.E.X. pneumolator; 2, by the addition of dead space (rubber hose) between mask and demand valve, and 3, by change of pressure in the high altitude chamber. Performance was measured by the Hecht contrast discrimination test and by a modification of the hand steadiness test described in a previous report (Fenn et al., 1946).

In the hand steadiness test, as originally described, the score was taken as the total number of contacts made by the subject during a 30 second test period. Preliminary experiments showed that this method of scoring may involve a serious error when the subject is very anoxic. Such a subject tends to allow the stylus to remain in contact with the plate for relatively long intervals of time during the test period.[2] The number of hits, which tends to be relatively few in such a case, is a poor measure of the subject's steadiness, because it is much easier for a subject to rest the stylus against the side of the hole than to hold it in the hole without touching. This problem has been solved by taking as the score, not the number of hits, but the total time during which the stylus makes contact in a period of 30 seconds. This time was measured in units of $\frac{1}{120}$ second by an A.C. impulse counter included in a circuit that was closed whenever the stylus made contact with the plate.

The general plan for an experiment was as follows. The subject entered the

[1] Work done under contract recommended by the Committee on Medical Research between the Office of Research and Development and the University of Rochester.

[2] In this test the subject endeavors to hold a stylus in a hole in a brass plate for a period of 30 seconds without making electrical contact with the sides of the hole. The stylus has a diameter of $\frac{3}{32}$" and the hole $\frac{1}{8}$". The elbow rests on the table but not the hand. The hole was $1\frac{1}{4}$" above the table in a brass plate tilted at an angle of 45° with the vertical. A very similar apparatus is sold by Stoelting and Co., Chicago, catalogue no. 19523.

high altitude chamber in which the illumination was set at a level which had previously been determined as being suitable for administering the contrast discrimination test. Following a period of 15 minutes, which was allowed for the subject to become adapted to this degree of illumination, the subject put on a mask and breathed air or oxygen from a demand system. The steadiness test and the contrast discrimination test were then administered alternately until three trials of each were completed. The scores thus obtained served as normal control values. In a few flights the control scores were obtained at 16,000 feet breathing oxygen instead of at ground level. In experiments where the use of the pneumolator was anticipated, the subject performed the control trials of the steadiness test while temporarily breathing on the pneumolator. This was done so as to have a control on the possible mechanical disturbance caused by the action of the pneumolator.

The subject with an observer was then taken to altitude where he proceeded to breathe air or oxygen either from a demand valve, or from a demand valve with added dead space, or from the G.E.X. pneumolator. The maximum altitude used in these experiments was 24,000 feet. After a period of from 5 to 10 minutes, allowed for the subject to become adjusted to the conditions, the tests were administered in the same fashion as at ground level. Upon completion of the second trial of the tests, an alveolar air sample, subsequently analyzed by the Haldane method, was taken. Following this a third trial of the tests was administered. Approximately half an hour was required to complete the series of measurements. Upon completion of the third trial of the tests, the chamber was changed to a new altitude or the setting of the pneumolator was changed or a different dead space was substituted, and another series of tests was administered and an alveolar sample was obtained.

During these experiments the subject wore electrodes connected to a cardiotachometer, and a heart rate record was obtained during the performance of each contrast discrimination test. In flights where anoxia was involved the subject also wore an ear oximeter. Unfortunately the oximeter readings proved to be so unreliable during most of these flights that it has seemed wise to discard the results. The cause of our difficulty seems to have been a faulty ear piece, since replaced by the manufacturer.

Eleven individuals (ten males and one female) served as subjects for these experiments. A total of 85 control runs and 171 experimental runs were completed.

RESULTS: One method of presenting the data is shown in figures 1 and 2. Each experimental series of three tests is represented by a symbol on one of these charts. The location of a symbol is determined by the alveolar carbon dioxide and oxygen tensions which existed during the performance. The type of symbol designates the probability, as determined by Fisher's "t" test, that the subject's scores in an experimental series of three trials of a test were not different from his control scores obtained breathing air or oxygen at ground level. The specific meaning of each type of symbol is indicated in the legend accompanying the figures.

This sort of graph with oxygen and carbon dioxide tensions as coordinates is advantageous in that contour lines representing equivalent altitudes and per cent saturations (nomogram of Henderson 1928) can be drawn readily. A line representing the normal composition of alveolar air from the data of Boothby has been added for reference.

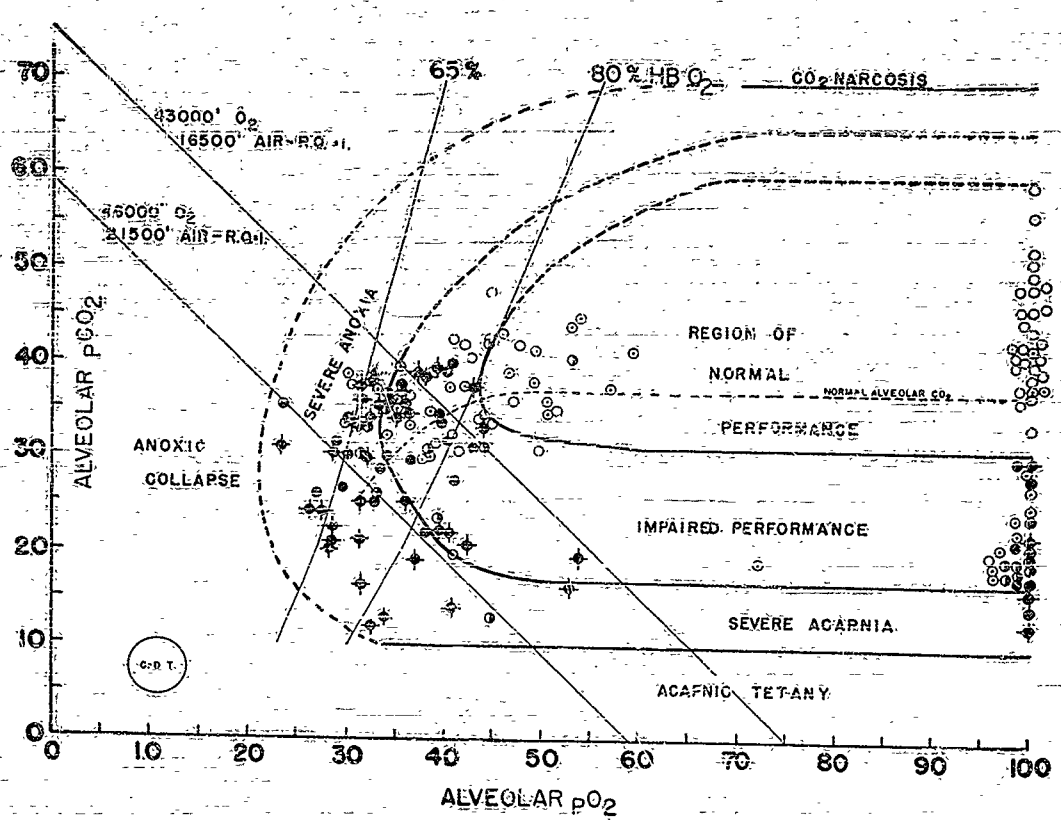

Fig. 1. Relationship of alveolar gas composition to steadiness test performance. Ordinates: alveolar carbon dioxide tensions in millimeters of Hg. Abscissae: alveolar oxygen tensions in millimeters of Hg. Each type of symbol represents a probability (p) that a subject's experimental score was not different from his control score;

The blacker the symbol the lower the probability and the greater the certainty of abnormality.

Solid circle with cross, $p < 0.01$; solid circle, $p = 0.01$ to 0.05; half solid circle, $p = 0.05$ to 0.1; open circle with dot, $p = 0.1$ to 0.5; open circle, $p > 0.5$.

An attempt has been made to divide the charts into regions of normal performance and different sorts of impaired performance. Such regions can be determined only very roughly by the data at hand, and the more uncertain regions are bounded by dotted lines. Certain tentative conclusions are indicated by these diagrams.

1. Following along any given pCO_2 value from right to left the performance becomes worse, i.e., anoxia does not appear to antagonize acapnia.

2. Starting at a normal pCO_2 level of 40 mm. and following any given per cent saturation line to lower pCO_2 values the performance becomes worse and never better, i.e., acapnia does not antagonize anoxia.

3. Thus acapnia and anoxia are additive or synergistic rather than antagonistic in their effects on these performance tests.

4. On the other hand, if one starts at a normal pCO_2 value of 40 mm. and follows down a given altitude diagonal to lower pCO_2 values the performance may improve over a certain range and then grow worse. There is, therefore, an optimum value or region of values of alveolar gas composition at each altitude for the best performance.

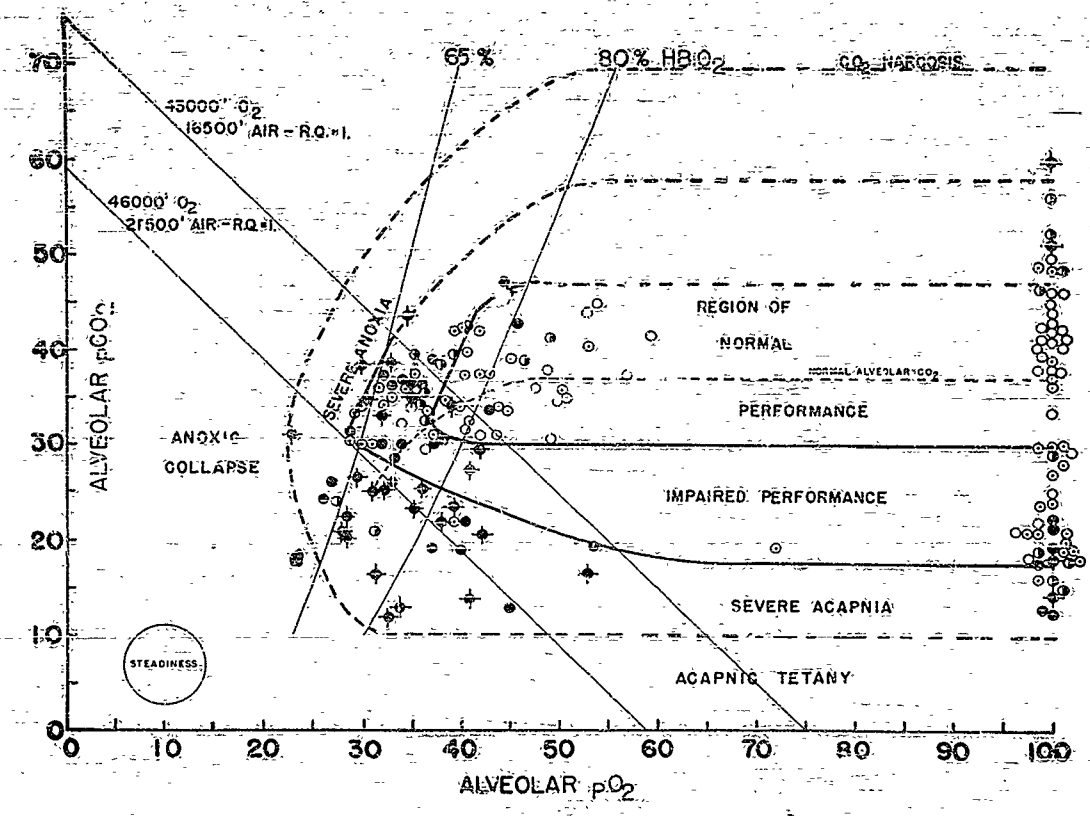

Fig. 2. Relationship of alveolar gas composition to contrast discrimination test performance. Co-ordinates and symbols as in figure 1. In general the blacker the symbol the greater the probability that the observed performance differed significantly from normal.

It should be emphasized that these conclusions and the regions bounded on the charts are tentative. It is obvious that a much larger number of tests would be needed to establish such a diagram with certainty.

Another method of treating the data which leads to the same general conclusions listed above attempts, in addition, to analyze performance impairment

into anoxic and acapnic components. Tables 1 and 2 were constructed for this purpose. For these tabulations the mean of the three trials of a test taken under a given set of conditions was taken as the score.

TABLE 1

Hand steadiness test scores as related to alveolar air compositions

pCO_2 / pO_2	<15				15–24.9					25–34.9					35–50				
	pCO_2	pO_2	Score	n	pCO_2	pO_2	Score	SDM	n	pCO_2	pO_2	Score	SDM	n	pCO_2	pO_2	Score	SDM	n
<30					22.4	27.8	1212	262	5	29.9	27.9	783	222	4					
30–34.9	12.4	33.2	2705	2	18.9	31.3	1915		2	31.3	33.5	779	122	15	37.7	32.7	826	147	8
35–39.9					22.1	37.8	1681	425	5	31.4	40.4	940	73	11	37.6	36.6	810	200	12
40–49.9	13.4	42.8	2111	2	20.6	41.2	1269		3	31.6	43.2	611	135	10	39.9	42.8	323	70	16
50–75					18.3	59.4	1056		3	34.9	50.8	209		2	40.6	54.6	177	82	6
100	13.2		1150	3	19.5		480	89	24	30.2		215	89	8	42.3		177	14	111

The heading of each horizontal row indicates the range of alveolar oxygen tension in millimeters Hg existing when the test scores entered in the row were obtained. The main headings of the vertical columns similarly indicate ranges of alveolar carbon dioxide tension. The sub-headings of the columns have the following meaning.

pCO_2, the average alveolar carbon dioxide tension in millimeters of Hg.

pO_2, the average alveolar oxygen tension.

Score, the mean of all scores in a particular range.

SDM, the standard deviation of this mean. (Calculated only when the mean was based on 5 or more cases.)

n, the number of individual scores (each individual score being the average of three trials) on which the mean score was based.

TABLE 2

Contrast discrimination test scores as related to alveolar air composition

pCO_2 / pO_2	<15				15–24.9					25–34.9					35–50				
	pCO_2	pO_2	Score	n	pCO_2	pO_2	Score	SDM	n	pCO_2	pO_2	Score	SDM	n	pCO_2	pO_2	Score	SDM	n
<30					22.4	27.8	24.3	1.17	5	29.6	27.9	16.5	1.72	8					
30–34.9	12.4	33.2	25.5	2	18.9	31.3	26.2		2	31.4	33.4	15.2	1.14	16	37.7	32.4	14.0	1.69	9
35–39.9					22.1	37.8	19.9	1.93	5	31.4	40.4	11.7	1.76	11	37.6	36.6	14.3	1.70	12
40–49.9	13.4	42.8	19.4	2	20.6	41.2	18.2		3	31.6	43.2	5.2	1.87	9	40.3	43.7	10.4	1.10	19
50–75					18.3	59.4	16.1		3	34.9	50.8	5.7		2	40.6	54.6	10.1	1.41	6
100	13.4		16.5	2	20.0		12.4	1.58	21	29.7		10.1	2.50	6	42.3		6.7	.33	84

The legend of table 1 applies.

Each value entered in these tables is the average of all scores obtained within the range of conditions indicated by the headings of the vertical columns and the horizontal rows. Examination of the columns of these tables indicates that, in general, performance grows worse as the alveolar oxygen tension is lowered in each of the ranges of alveolar carbon dioxide tension. A similar examination of the horizontal rows shows a tendency for performance to deteriorate as the alveolar carbon dioxide tension falls within each range of alveolar oxygen ten-

sions. This suggests the possibility of plotting performance scores against one of the independent variables and indicating the second independent variable by contour lines. This has been attempted in figures 3 and 4 in which performance test scores are plotted against alveolar oxygen tensions with ranges of

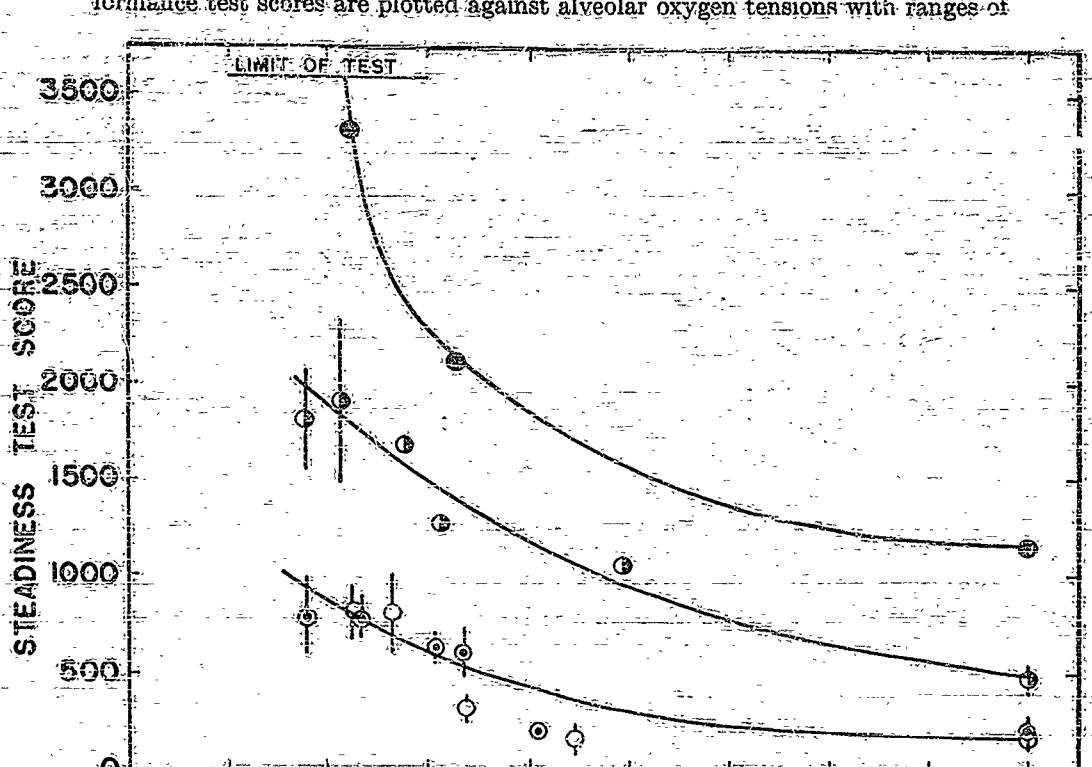

Fig. 3. Steadiness test scores as related to alveolar air composition. Based on the data shown in table 1.

Ordinates: Steadiness test scores in $\frac{1}{120}$ second.

Abscissae: Alveolar oxygen tension in millimeters of Hg.

The types of symbols designate the range of alveolar carbon dioxide tensions as follows: solid circles, < 15 mm. Hg; half solid circles, 15–24.9 mm. Hg; open circle plus center dot, 25–34.9 mm. Hg; open circles, 35–50 mm. Hg.

The vertical lines through some of the points indicate the standard deviation of the mean.

Since the test trials were 30 seconds in duration, the maximum possible score would be 3600 as indicated by the horizontal line on the graph.

alveolar carbon dioxide tensions bounded by contour lines. These graphs show that with lowered oxygen tension, performance becomes worse in all ranges of carbon dioxide tensions. The slope of the lines rapidly becomes steeper as the oxygen tension falls below 40 mm. Hg.

The lowest of the family of curves in each graph is of particular interest.

These curves may be considered as pure anoxia curves since they fit the points obtained with alveolar carbon dioxide tensions in the 35–50 mm. range which is within the normal ground level range. The points for the 25–34.9 mm. are hardly different. This confirms our previous conclusion (Fenn et al., 1946) that the alveolar carbon dioxide tension may be lowered to 25–30 mm. in the average

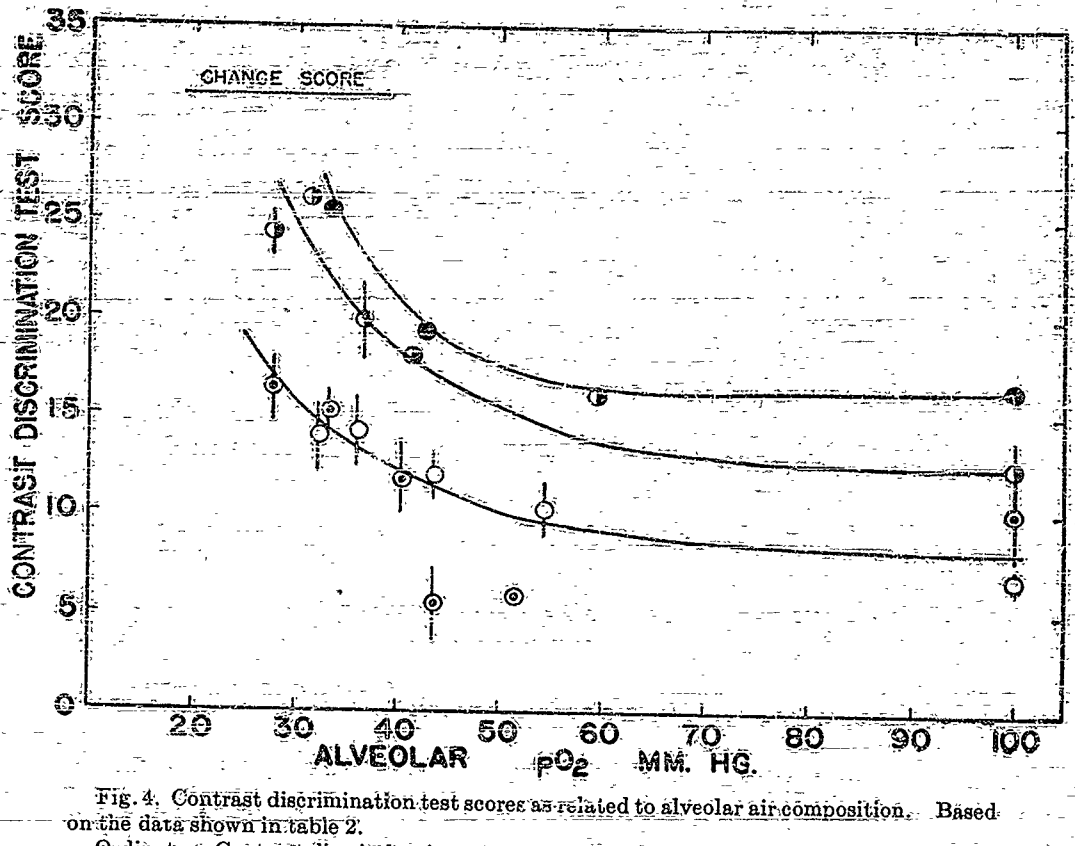

Fig. 4. Contrast discrimination test scores as related to alveolar air composition. Based on the data shown in table 2.

Ordinates: Contrast discrimination test score. The maximum possible score is 36. The score that would be obtained by chance is 31.5.

Abscissae: Alveolar oxygen tensions in millimeters of Hg.

The meaning of the types of symbols is the same as for figure 3.

individual without serious impairment of performance as judged by these particular tests.

The points obtained in the ranges of CO_2 tensions below 25 mm. are considerably elevated above the pure anoxia curve. The performance impairment represented by these elevated points is due to the combined effects of anoxia and acapnia.

The data in the lowest row of tables 1 and 2 show the effect of acapnia alone on performance, because they were obtained with alveolar oxygen tensions of

100 or above. Pure acapnia curves constructed from these data are shown in figures 5 and 6.

If the effects of anoxia and acapnia are simply additive, it should be possible to determine how much of the performance impairment represented by any point in figures 3 or 4 is due to anoxia, by subtracting the increment of score that would have been caused by the degree of acapnia existing. Accordingly the following procedure was followed with each score entered in table 2.

1. The pCO_2 existing when the score was obtained was noted.
2. The increment of score that this pCO_2 would cause was read from figure 5.
3. This increment was subtracted from the original score.
4. The corrected score was plotted against the alveolar oxygen tension.

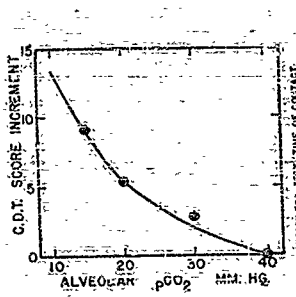

Fig. 5

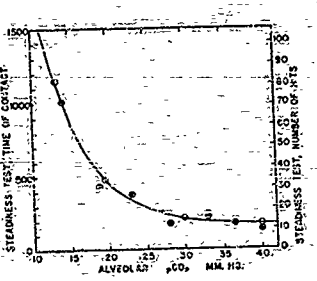

Fig. 6

Fig. 5. The effect of acapnia on contrast discrimination test performance. Plotted from the data of the last row of table 2.

Ordinates: Increments of test score above normal.

Abscissae: Alveolar carbon dioxide tension in millimeters of Hg.

Fig. 6 The effect of acapnia on steadiness test score.

Abscissae: Alveolar carbon dioxide tension in millimeters of Hg.

Ordinates: The scale on the left gives steadiness test scores as time of contact in units of $\frac{1}{120}$ second during a 30 second test period and applies to the open circles which represent the data in the last row of table 1. The scale on the right gives steadiness test scores as number of hits during a 30 second test period and applies to the closed circles which represent the data from another series of experiments described in a previous report (Fenn, et al., 1946). Those points have been plotted here to show that the two methods of scoring the steadiness test give similar results as far as acapnia is concerned.

Figure 7 shows that this procedure has resulted in fitting all the points reasonably well to the pure anoxia curve for the contrast discrimination test. It is justifiable, therefore, to conclude that the effects of acapnia and anoxia on this type of performance are approximately additive.

In the case of the steadiness test data, however, the "corrected" scores gave a much poorer fit. Most of the points lay well above the pure anoxia curve, indicating that the correction for acapnia was inadequate. Consequently, a modified procedure was applied to each of the steadiness test scores entered in table 1.

1. The pCO_2 existing when the score was obtained was noted.
2. The *multiple* of the control score that this pCO_2 would give was determined from figure 6.

3. The original score was divided by this multiple.

4. The corrected score was plotted against the alveolar oxygen tension.

The result is shown as figure 8. The fact that this method resulted in a reasonably good fit of all the steadiness test scores to the pure anoxia curve indicates that the steadiness test score is a logarithmic rather than an arithmetic function of performance.

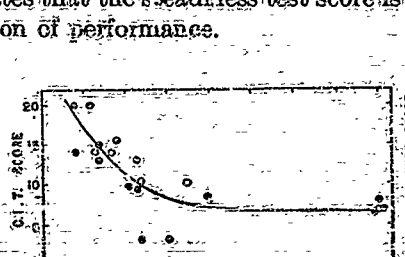

Fig. 7

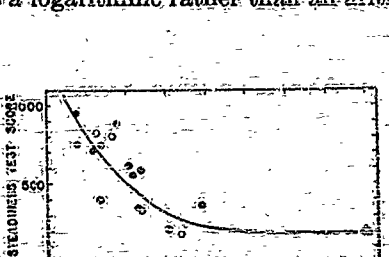

Fig. 8

Fig. 7. The effect of anoxia on contrast discrimination test score.

Ordinates: Contrast discrimination test scores.

Abscissae: Alveolar oxygen tensions in millimeters of Hg.

Open circles: Scores obtained with alveolar carbon dioxide tensions between 35-50 mm. Hg.

Closed circles: Scores obtained with alveolar carbon dioxide tensions below 35 mm. but corrected for the effects of acapnia by the method described in the text.

Fig. 8. The effect of anoxia on steadiness test scores.

Ordinates: Steadiness test scores as time of contact in units of $\frac{1}{120}$ second during a 30 second test period.

Abscissae: Alveolar oxygen tensions in millimeters of Hg.

Open circles: Scores obtained with alveolar carbon dioxide tensions in the range of 35-50 mm. Hg.

Closed circles: Scores obtained with alveolar carbon dioxide tensions below 35 mm. but corrected for acapnia by the method described in the text.

Having separated the effects of acapnia and anoxia and having determined the nature of their combined action on the test scores, it is possible to determine a theoretical score for any combination of alveolar oxygen and carbon dioxide tensions, or to construct isopleths of constant score on a pCO_2-pO_2 grid as has been done in figures 9 and 10. Such lines were constructed as follows:

1. The desired score was chosen.
2. Reference to the pure acapnia curve established the right hand end of the line (at pO_2 = 100 mm.).
3. Reference to the pure anoxia curve established the left hand end of the line (at pCO_2 = 40 mm.).
4. Intermediate points were established by choosing an oxygen tension, determining from the pure anoxia curve what score would be obtained at this tension, and then determining from the pure acapnia curve what the pCO_2 would have to be to give an increment (in the case of the contrast discrimination test) or a multiple (in the case of the steadiness test) that would yield the arbitrarily chosen score when added to or multiplied by the pure anoxia score.

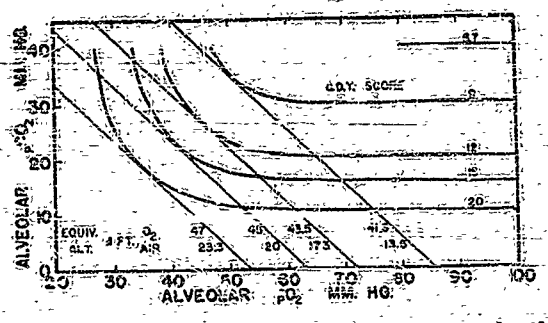

Fig. 9. The relationship of contrast discrimination test scores to alveolar air composition and equivalent altitude.

Ordinates: Alveolar carbon dioxide tensions in millimeters of Hg.

Abscissae: Alveolar oxygen tensions in millimeters of Hg.

Curved lines are isopleths of constant score constructed by the method described in the text.

Diagonals represent the equivalent altitudes indicated for breathing oxygen and for air when the R.Q. = 1.

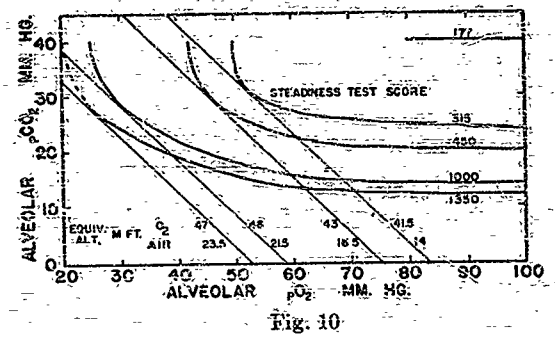

Fig. 10

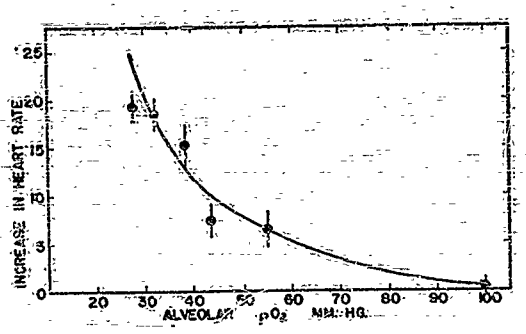

Fig. 11

Fig. 10. The relationship of steadiness test scores to alveolar air composition and equivalent altitude.

Ordinates: Alveolar carbon dioxide tensions in millimeters of Hg.

Abscissae: Alveolar oxygen tensions in millimeters of Hg.

Curved lines are isopleths of constant score constructed by the method described in the text.

Diagonals represent the equivalent altitudes indicated for breathing oxygen and for air when the R.Q. = 1.

Fig. 11. Heart rate increase as a function of alveolar oxygen tension. Plotted from the data in the last main column of table 3.

Ordinates: Increase in heart rate above the control rate in beats per minute.

Abscissae: Alveolar oxygen tensions in millimeters of Hg.

The vertical lines through the points indicate the standard deviation of the mean.

By constructing an altitude diagonal which is tangent to an isopleth, the optimal alveolar air composition for this altitude is established by the co-ordinates of the point of tangency. When oxygen is breathed only one altitude

diagonal can be drawn tangent to a given isopleth. If air is the inspired gas, however, a multitude of such lines can be drawn, because of the R.Q. effect. The diagonals drawn in figures 9 and 10 represent air breathing altitudes if the R.Q. is equal to 1, or oxygen breathing altitudes at any R.Q.

That the two tests employed have different optimums is obvious from a comparison of figures 9 and 10. At the altitude of 47,000 feet, for example, the optimum pCO_2 for the steadiness test is 27 mm., but for the contrast discrimination test it is at 18 mm. These values should not be taken too seriously as far as their absolute magnitudes are concerned, but it seems fair to draw the conclusion that a degree of hyperventilation greater than the normal for the average individual at altitude will not improve his steadiness test score but will

TABLE 3

Heart rate change as related to alveolar air composition

pO_2	<15				15–24.9				25–34.9				35–50				ALL			
	pCO_2	pO_2	Rate	n	pCO_2	pO_2	Rate	n	pCO_2	pO_2	Rate	n	pCO_2	pO_2	Rate	n	pO_2	Rate	SDM	n
<30					23.4	27.9	+21.4	5	29.0	27.9	+18.0	8					27.9	+19.4	1.59	13
30–34.9	19.4	32.2	+19.5	2	18.9	31.3	+23.5	2	31.1	32.5	+17.5	15	37.7	32.4	+19.2	9	32.4	+18.5	1.51	28
35–39.9					21.7	37.4	+12.0	4	31.5	40.7	+15.3	10	37.3	36.7	+16.3	11	38.4	+15.2	2.33	25
40–49.9	15.4	28.8	+13.0	2	20.6	41.2	+7.0	3	31.9	43.1	+11.8	9	41.1	44.3	+4.3	15	43.5	+7.5	1.67	29
50–75					18.8	59.4	+4.5	5	34.5	50.5	+6.0	2	41.3	64.1	+9.8	5	55.0	+6.5	1.93	12
100	12.4		−3.0	2	20.2		+1.8	20	30.6		+1.1	7	42.3		+1.2	26		+0.4	0.95	55

The heading of each horizontal row indicates the range of alveolar oxygen tension in millimeters of Hg existing when the heart rate measurements were obtained. The main headings of the vertical columns similarly indicate ranges of alveolar carbon dioxide tension. The sub-headings of the columns have the following meanings:

pCO_2, the average alveolar carbon dioxide tension in millimeters of Hg.

pO_2, the average alveolar oxygen tension.

Rate, the mean change with respect to normal of all heart rates measured in the indicated range.

n, the number of determinations (each determination being the average of three measurements) on which the mean change in heart rate was based.

The last main column is a summation of results for all ranges of carbon dioxide tensions. The sub-heading, SDM, in this column refers to standard deviation of the mean.

improve his contrast discrimination test score. There is an optimum alveolar pCO_2 at each altitude for a given type of performance, but the optimum for another type of performance is likely to be different.

The conclusion that one should not hyperventilate below a pCO_2 level of 27 mm. at 47000 feet is borne out by a series of flights which we have made to 30000 and 46000 feet. Measurements were made of the alveolar pCO_2 level and the hand steadiness by the test described. Data are available on 4 subjects at each altitude. At 46000 feet the steadiness begins to decrease below 25 or 28 mm. Hg pCO_2 in spite of the concomitant increase of pO_2. Furthermore, for the same pCO_2 level, the hand is always more unsteady at the higher altitude than at 30000 ft. and is more unsteady at 46000 ft. at any pCO_2 level than at ground level breathing normally. These results also confirm therefore the idea that anoxia and acapnia are additive in their effects.

Relationship of heart rate to alveolar gas tensions. Table 3 shows the mean change in heart rate obtained in various ranges of alveolar oxygen and carbon

dioxide tensions. The results show that heart rate is definitely related to alveolar oxygen tension, but is not significantly changed by alterations in the carbon dioxide tension over the limits investigated. Consequently, heart rate increments for all ranges of carbon dioxide tensions within each range of oxygen tension have been averaged as indicated in the extreme right hand column of the table. These values are shown plotted against the alveolar oxygen tension in figure 11.

TABLE 4

Summary of experiments in which subjects breathed naturally

Alt.	n	pCO_2	pO_2	R.Q.	Time	S.T.	C.D.T.	H.R.	Sat.
M.ft.		*mm.Hg*	*mm.Hg*		*min.*				*per cent*
G.L.	18	38.1				147	6.7	0	
12	19	39.8	47.1	0.88	22	157	10.0	+5.1	81
16	7	33.8	40.8	0.94	28	455	12.6	+15.5	78
18	18	33.7	34.0	0.94	22	405	13.8	+15.1	69
20	4	31.9	34.0	1.12	19	1070	17.8	+20.0	71
22	2	29.2	27.9	1.00	33		21.9	+18.0	64

The column headings have the following meanings:

Alt., simulated altitude in thousands of feet.

n, the number of experiments performed.

pCO_2, the alveolar carbon dioxide tension in millimeters of Hg.

pO_2, the alveolar oxygen tension in millimeters of Hg.

R.Q., the respiratory quotient as calculated from the alveolar oxygen and carbon dioxide tensions.

Time, the time in minutes which had been spent at altitude when the alveolar sample was taken.

S.T., steadiness test score.

C.D.T., contrast discrimination test score.

H.R., change in heart rate with respect to normal.

% Sat., the per-cent saturation of arterial blood as estimated from the alveolar oxygen and carbon dioxide tensions with the aid of Henderson's nomogram.

G. L., ground level.

In so far as heart rate increment is a criterion of added circulatory strain, these results indicate that although anoxia may act as a considerable stress acapnia does not.

Variations in performance, alveolar gas composition, and heart rate with altitude. Some of the experiments described above were performed with the subject breathing naturally from the demand regulator. The number of such runs at some of the altitudes is small, but it seems worth while to summarize the results briefly, because they indicate what individuals will do at air breathing altitudes when left to their own resources.

Table 4 shows the mean values obtained at each altitude for the various quantities measured or calculated, and figure 12 shows the same results in graphic form. The values for per cent saturation are estimated from the alveolar oxygen and carbon dioxide tensions, and are not oximeter readings. As mentioned above the behavior of our oximeter was unsatisfactory during this series of flights.

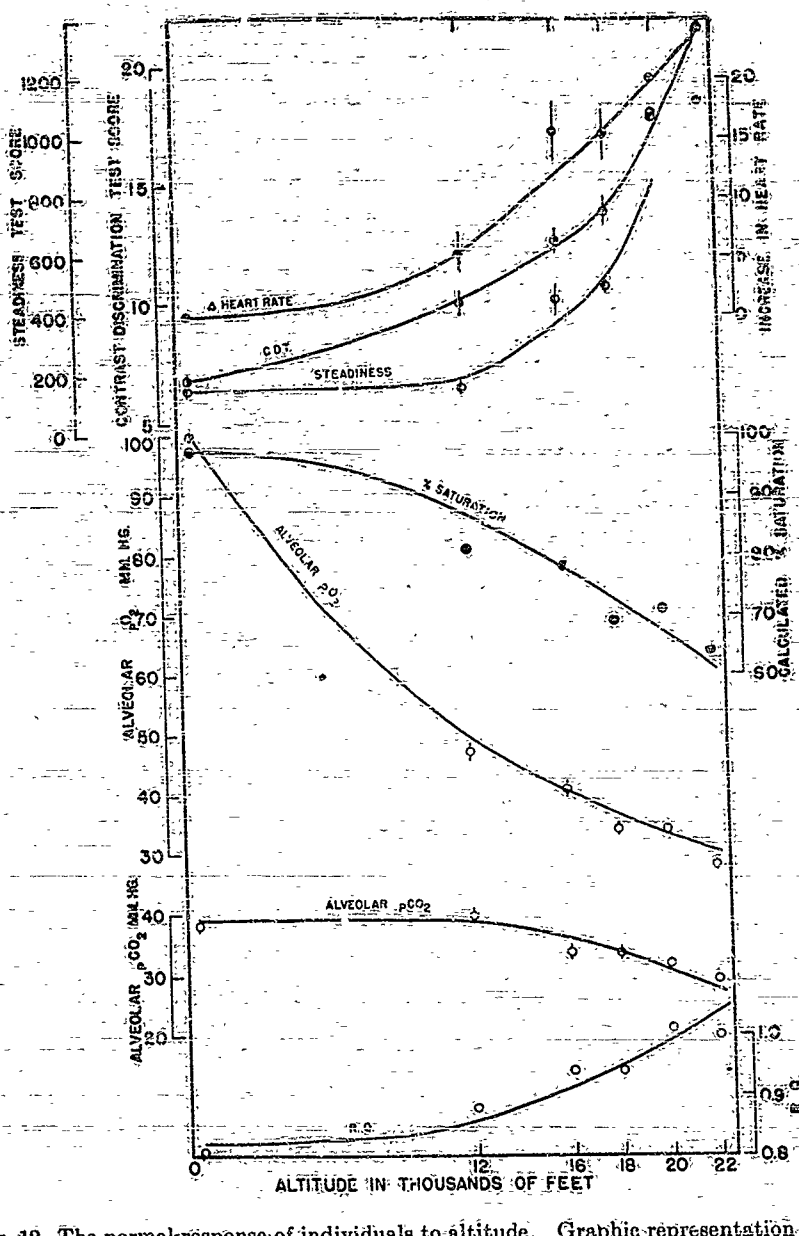

Fig. 12. The normal response of individuals to altitude. Graphic representation of the data in table 4. The vertical lines through some of the points indicate the standard deviation of the mean values represented by the points.

The values shown for alveolar air composition, in general, are in good agreement with the much more extensive series of Boothby. (See Helmholz et al., 1944.) Our data fail to show any lowering of the pCO_2 at the 12,000 foot altitude,

but this may be due to the fact that the ground level values and the altitude values were not necessarily obtained on the same subjects on the same day.

The 12,000 foot altitude shows a small but significant effect on the contrast discrimination test and on heart rate, but leaves the steadiness test score unchanged from the ground level value. The higher altitudes show progressively greater effects on all items measured, with performance deteriorating very rapidly above 13,000 feet. The highest altitude studied, 22,000 feet, is probably close to the maximum at which most unacclimatized individuals will maintain consciousness for a half hour period. Similar effects of altitude have been described by McFarland (1938), who used choice reaction time, a color naming test, a code test, and a memory test as criteria of performance. He found that the mean impairment of performance was not statistically significant at altitudes below 12,000 feet.

The question may be asked as to whether the effect of altitude on the performance of individuals breathing naturally is purely an anoxic effect or whether the hyperventilation which normally accompanies the anoxia at altitudes above 12,000 feet produces significant acapnic effects. A comparison of the results shown in figure 12 with the pure anoxia curves in figures 7 and 8 indicates that the performance impairment of altitude is essentially a matter of anoxia alone. The fact that the alveolar pCO_2 drops below 30 mm. only at the highest altitude, 22,000 feet, (and only slightly below even at this altitude) would also indicate, on the basis of the pure acapnia curves, that acapnia could be, at most, only a very small factor. It is probable, of course, that a few, relatively rare individuals may spontaneously hyperventilate enough to experience acapnic impairment, but the large majority will suffer only from anoxia when their breathing is guided by their own reflexes at air breathing altitudes.

We wish to acknowledge the kindness of Mr. John H. Clough, President of the General Electric X-Ray Corporation, who placed the pneumolator at our disposal. We are grateful also to Dr. Selig Hecht for providing us with the contrast discrimination test used in these studies.

It is a pleasure also to offer our thanks to the many subjects who have faithfully and willingly served in these experiments, particularly Mary Hodge, Florence Neiman, M. Brontman and four members of C.P.S. Unit No. 115, T. Horvath, H. Mitchell, J. Heil, and A. Culp.

SUMMARY

1. Performance (contrast discrimination test and steadiness test) and heart rates of 11 subjects were measured over a wide range of alveolar oxygen and carbon dioxide tensions. A total of 171 half-hour experiments and 85 control runs were made.

2. The results are plotted on an alveolar pCO_2-pO_2 grid, and regions of normal performance and of various kinds of impaired performance are indicated.

3. A method for analyzing performance impairment into anoxic and acapnic components is described.

4. The results indicate the following conclusions:

a. Acapnia and anoxia are additive rather than antagonistic in their effects on performance.

b. There exists at each altitude an optimum alveolar gas composition for best performance.

c. This optimum may be different for different types of performance.

d. Heart rate is increased by anoxia, but is not consistently affected by acapnia.

e. Performance impairment in most individuals breathing naturally at air-breathing altitudes is essentially a matter of anoxia alone.

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The Effects of Hypocapnia on Performance

By H. Rahn, A. B. Otis, Mary Hodge, M. A. Epstein, S. W. Hunter and Wallace O. Fenn

AT ALTITUDES high enough to produce severe anoxia, the physiological problem is to divide the total dry gas tension in the alveoli in the most advantageous way between oxygen and carbon dioxide by selecting an optimum ventilation rate. As an initial step in determining what this optimum rate is at different altitudes it seemed important to measure the effects of acapnia or hypocapnia alone. Since no measurements suitable for our purposes seemed to be available in the literature, we undertook a series of experiments in a high altitude chamber at a simulated altitude of 30,000 feet. When breathing oxygen at this level the alveolar pO_2 is higher than it is at ground level so that no anoxia can enter into the picture. The low density of the air, however, makes it very easy to overventilate when the oxygen is supplied through a pneumolator. This is an apparatus made by the General Electric X-Ray Corporation which was kindly loaned to us for experimental purposes. Using this device, oxygen is supplied to the mask until the pressure in the mask and lung reaches a critical level which is usually set somewhere between 10 and 30 cm. of water. When the mask pressure reaches this point the inflow of oxygen ceases and an expiratory port is opened through which the subject expires at a rate determined by an adjustable gate. The more rapid the expiration and the higher the peak pressure the greater the degree of acapnia. With two adjustments of the apparatus therefore the alveolar pCO_2 could be set at any desired level and maintained there for long periods.

In these flights the subject breathed oxygen from a Pioneer Demand System during the ascent and for a period of twenty to thirty minutes after arrival at 30,000 feet. During this period an alveolar air sample was taken for Haldane analysis, and two or more trials of one of the performance tests were made. The scores obtained at this time were taken as a baseline. The subject next hyperventilated with the pneumolator at some previously chosen rate and pressure, an alveolar sample was taken, and further trials of the test were made. In most flights the setting of the pneumolator was then changed to give a different degree of hyperventilation which was maintained until another set of trials was completed, and alveolar samples obtained. In most cases the test was also administered at ground level before and/or after the flight. During some of the flights two of the performance tests were completed by administering trials of the two tests alternately.

Work done under contract recommended by the Committee on Medical Research between the Office of Research and Development and the University of Rochester.

As measures of the effects of acapnia we used the subjective symptoms as well as four performance tests as follows: the hand steadiness, choice reaction time, multiplication time, contrast discrimination test. These will be described in turn.

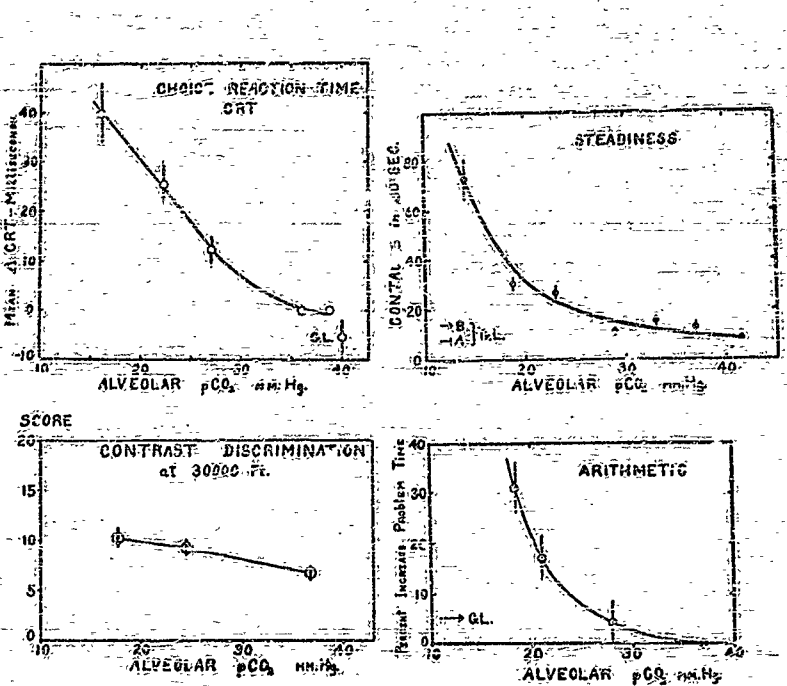


Fig. 1. The effects of lowered alveolar pCO_2 on performance. Vertical lines through the experimental points represent probable errors of the means. G.L. means ground level score, before (B) and after (A). In D the G.L. score (arrow) was higher than the initial score at 30,000 ft. which was taken as the base line.

STEADINESS TEST

In this test the subject endeavored to hold a metal stylus in a hole in a brass plate without allowing the stylus to come in contact with the plate. The plate was set with the hole 1¾ inches above the table and tilted away from the subject at an angle of 45 degrees with the vertical. The stylus, which was fitted with an insulated handle, was 3/32 inch in diameter; the hole was ⅛ inch in diameter. Whenever the stylus touched the plate an electrical circuit including an impulse counter was completed, so that every contact made by the subject was registered by the impulse counter. Each trial was of thirty seconds' duration and the number of contacts made during this period was taken as the subject's score for the trial. In taking the test the subject held the handle of the stylus in his fingers 4 inches from the tip and was permitted to rest his elbow but not his hand on the table.* The experiments with this test include 318 trials

*A very similar apparatus is sold by C. H. Stoelting Co., Chicago. catalogue No. 19523.

TABLE I. STEADINESS TESTS, SUMMARY OF DATA

pCO_2 Range mm. Hg	Mean pCO_2 mm. Hg	Mean Score	Std. Dev. of Mean	Mean Duration Min.	No. of Tests	Incidence of Acapnia
40–45	41.5	7.9	1.5	30	29	
35–40	37.4	12.8	2.5	33	49	
30–35	33.0	15.2	2.7	27	23	
25–30	28.1	11.1	1.4	29	48	
20–25	23.0	26.0	4.0	25	53	26.3%
15–20	18.7	30.5	3.2	25	55	66.7%
10–15	14.1	72.6	11.6	26	13	100 %
Ground level pre-flight		14.2	4.3		30	
Ground level post-flight		8.5	1.4	16	22	

by ten different subjects during twenty-nine flights. The results are summarized in Figure 1B and Table I. For purposes of statistical analysis the data have been grouped according to the alveolar carbon dioxide tension as indicated in the table. For each of these groups the mean score, standard deviation of the mean, duration of the stay at the indicated pCO_2 level, the number of tests, and the incidence of acapnia are given. The test scores plotted against the pCO_2 in Figure 1 show a progressive increase of score or deterioration of performance as the pCO_2 falls. The mean scores of tests given at ground level before and after flights are indicated by arrows on the graph. Although the mean score for the tests given before flights is higher than the mean for postflight tests the difference is not statistically significant.

In general we have found this test more sensitive to acapnia than to anoxia. In using it for later experiments we have added to the circuit a 60-cycle impulse counter which in effect measures the total duration of contact. This avoids the possibility of obtaining a low score by maintenance of continuous contact. Actually in a co-operative subject we have not encountered this difficulty.

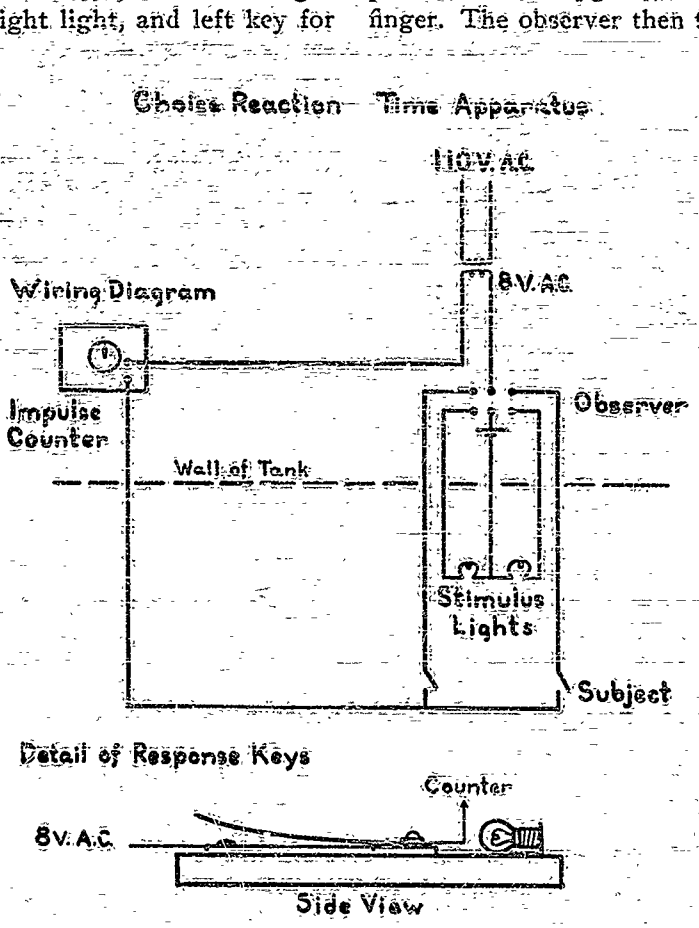
CHOICE REACTION TIME TEST (CRT)

The apparatus used for measurement of reaction time with choice was a portable one designed and built in this laboratory. It uses a Cenco impulse counter to measure the reaction time. Sixty cycle current is stepped down to 8 volts and fed through a circuit in which two response keys and a stimulus switch are included. A separate dry-cell circuit is connected also to the stimulus switch and two small 2-volt light bulbs in front of the subject's response keys (Fig. 2).

The observer outside the low pressure chamber operates a double-pole, double-throw switch with which he can light either bulb and close the counter circuit. The subject must at this time have both keys depressed to start the counter. The response keys are made of thin strips of sheet metal. Both keys and lights are mounted on a small platform which is placed before the subject in the chamber.

In all the determinations of choice reaction time which we are now reporting the choice used was right key for right light, and left key for left light. It is to be noted here that the lights do not go off when the subject raises his key. The counter, however, does not stop unless the correct key is lifted.

Before a series the subject was told to get ready for a reaction and pressed both keys with his index finger. The observer then threw the stimulus switch, one light lighted, and the subject responded by raising the appropriate key, thus stopping the counter. The observer recorded the counter reading, and turned off the light by raising the stimulus switch. When the light went out the subject pressed his keys again, and was ready for another trial.



In the present series of flights, reaction times were measured at 5- to 10-minute intervals during the flight. Each such measurement consisted of 25 tests made as rapidly as possible.

A unit on the counter corresponds to 1/120 of a second, since it is designed to respond 120 times a second to 60-cycle current. Scale readings were converted to milliseconds in every case. Errors were announced by another observer and recorded, but not included in the averages. For each series 25 determinations without error were made.

We made a few trial runs measuring CRT before this series of flights was started, and noticed a considerable preliminary learning effect. To overcome this three or four series of 25 tests were run at ground level before each flight. The results of these tests were not recorded.

RESULTS

The CRT test has been given to ten different subjects during twenty-one flights. For purposes of analysis the score obtained by the subject while breathing from the Demand Regulator during the period just after arrival at 30,000 feet is taken as the baseline score in each flight. Figure 1A is a plot of the average increment in the choice reaction of all subjects against alveolar pCO_2. On each flight the average increment in CRT of the subject over his normal baseline on that flight was determined, and the increments of the various subjects in turn were averaged. To make this plot we have grouped the data into arbitrary levels of pCO_2, namely, 40-45 mm. Hg, 30-39 mm. Hg, 25-30 mm. Hg, 20-24 mm. Hg, and 14-19 mm. Hg. It might be noted here that the plot of increment in reaction time presents a more faithful picture of the relationship between CRT and pCO_2 than a plot of actual reaction time and pCO_2. This is because plotting increments does away with variations in the normal baseline of various subjects, which were large. The shape of the curve found by plotting reaction time against CO_2 tension will depend on which subjects reach each CO_2 level, while in a plot of increments the selection of subjects does not influence the shape of the curve.

From Figure 1A it can be seen that at a pCO_2 level of 20-25 mm. Hg there was an average increase of 25.6 milliseconds (8.7 per cent) in choice reaction time. At a level of 15-20 mm. Hg the increase amounted to 39.9 milliseconds (13.6 per cent). At pCO_2 levels above 25 mm. Hg the increase was slight—4.1 per cent at 25-30 mm., and 0 at 35-40 mm. The recovery values obtained at ground level after the flight are not significantly different from the original baseline. That the increments at acapnic levels (15-25 mm. Hg) are significant is shown by the probable errors of each mean, as indicated on the graph. The data from these tests are summarized in Table II.

MULTIPLICATION-TIME TEST

In order to test the subject's ability to perform more complex operations requiring a longer period of concentrated effort, an arithmetic test was devised. The problem was to multiply two five digit numbers (by longhand) in the shortest possible time. The subject clocked the time required on a stopwatch, the score was obtained by adding to this time five seconds for each error in multiplication or addition. The error allowance is entirely arbitrary; a different method of evaluation might give somewhat different

TABLE II. SUMMARY OF CHOICE REACTION TIME DATA—AVERAGES AND STANDARD DEVIATIONS

Range pCO_2 mm. Hg	Mean pCO_2 mm. Hg	Mean C.R.T. m.s.	St. Dev. of Mean C.R.T. m.s.	Mean C.R.T. m.s.	St. Dev. of Mean C.R.T. m.s.	Mean of Duration min.	No. of Tests	No. of Flights	Incidence of Acapnia
40–45	41.2	294	12.5	0		33.8	1000	11	
30–39	35.9	298	13.8	= 23		23.1	775	11	
25–30	26.8	312	12.5	12.4	4.2	28.9	1000	15	0
20–24	22.2	320	21.4	25.8	5.9	25.6	825	10	36%
14–19	16.2	316	14.4	39.9	8.8	27.1	750	9	89%
Recovery (40)		290	11.0	= 5.6	5.0		1025	14	

TABLE III. MULTIPLICATION—TIME TEST, SUMMARY OF DATA

pCO_2 Range mm. Hg	Mean pCO_2 mm. Hg	Mean Score	Std. Dev. Mean Score	Mean %	Std. Dev. Mean %	Mean Duration Minutes	No. of Tests	Incidence of Acapnia
GL	(40)	131	11.0	5.4%	3.6%		19	
30.3–41.1	36.8	113	12.1	0		26	21	
25.7–34.1	28.1	114	15.4	4.2%	4.1%	25	13	0.0%
19.3–24.2	21.1	132	15.4	17.3%	4.0%	28	13	18.2%
14.5–19.1	18.6	144	20.0	31.3%	5.0%	29	13	92.4%
Recovery	(40)	115	10.7	5.5%	8.1%		15	

results. The problems were so chosen that no 1's or 0's were in the multiplier, and there was either a 2 or a 5, but not both. In a series of ground level trials, the sixteen problems used were found to be of approximately equal difficulty. It was also found that no improvement in score from day to day was found even though the same problems were used over and over again. In the majority of cases the subject completed three problems at each pCO_2 level and the results were averaged together to give the score for that point. In individual cases the number of problems varied from one to eight. In most of the flights a score was obtained at ground level before and after the flight, one at altitude without acapnia, and one at each of two levels of acapnia. In order to compare individuals with widely differing initial scores it was found best to use the percentage increment in the score. As a baseline we used the normal score at 30,000 feet without acapnia for the same flight or, where necessary, for another flight by the same subject. Eleven subjects were used on a total of twenty-five flights. In all but three flights acapnia caused an increase in the score over the 30,000 feet normal. In these three flights the baseline was inexplicably high but the other points showed the usual progressive increase in problem time with decrease of pCO_2.

The curve in Figure 1*D* shows the mean per cent increment in arbitrarily chosen ranges of alveolar pCO_2 with

TABLE IV. SUMMARY OF CONTRAST DISCRIMINATION TEST DATA

pCO_2 Range mm. Hg	Mean pCO_2 mm. Hg	Mean Duration Minutes	Number of Tests	Mean Score	Std. Dev. of Mean	Incidence of Acapnia
30–41	36.7	14.2	33	6.70	3.10	0
20–30	24.5	18.3	33	9.45	4.31	84.6%
15–20	17.8	17.5	23	10.35	5.51	92.3%

the standard deviation for each mean. Table III presents the data of the graph, together with means and standard errors for the actual scores in seconds, the mean duration at each acapnic level, and the number of points represented in the various means. In order to see if the duration of time at an acapnic level had any effect on the problem time, about two-thirds of the flights were analyzed for time increment between the first and second and the first and third problems done at each pCO_2 level. The analysis indicated that duration at these levels was not a factor, except in the ground level flights, where there was a slight decrease in time required between the first and third problems, probably due to learning. At acapnic levels there was, if anything, an improvement in score with duration of low pCO_2, but in no case could it be called significant.

CONTRAST DISCRIMINATION TEST

This test was designed by Dr. Selig Hecht of Columbia University to demonstrate impairment of contrast discrimination due to anoxia. We are indebted to Dr. Hecht for supplying us with the materials necessary for this test. It consists of a series of eighteen pairs of C's arranged around the perimeter of a disc. The disc can be rotated so that any pair of C's is visible through an opening in a sheet of cardboard covering the disc. Only one pair of C's is visible at one time, however. The problem for the subject is to locate the position of the break in each of the C's, and to record his decision on a special score sheet provided for this purpose. The subject is allowed a maximum of ten seconds for each pair of C's. The number of errors is taken as the score.

A constant source of illumination was assured for these tests by placing a voltage regulating transformer in the line supplying the lighting system of our chamber. Curtains were so arranged that no extraneous light came from the outside through the ports of the chamber. Preliminary tests were run to determine the proper level of illumination. Before each ascent the subject went inside the chamber and performed one or more practice tests. The scores on these tests were used only to make sure that the illumination was satisfactory and are not included in the results.

Seventeen flights were made during which the test was performed by nine different subjects. The data obtained are summarized in Table IV. The relationship of test scores to alveolar CO_2 tension is presented in Figure 1C. These results indicate that this test is not very sensitive to acapnia. The greatest change measured is not large,

nor is there a more rapid change as the pCO_2 drops below 25 mm. as was shown by the other performance tests.

These observations are summarized in Figure 3, which indicates the percentage incidence of subjective symptoms at various ranges of alveolar carbon dioxide tensions. This graph shows that no symptoms were reported at CO_2 tensions above 25 mm. Hg. On the other hand, at tensions less than 15 mm., 100 per cent of subjects showed symptoms. It should be pointed out that although the data for the range, 10 to 15 mm., represents only two subjects, we have observed numerous subjects in other flights at CO_2 levels in this range, and symptoms were present in all cases. In the ranges, 15 to 20 mm. and 20 to 25 mm., only part of the subjects reported symptoms, but both the incidence and the degree of severity is

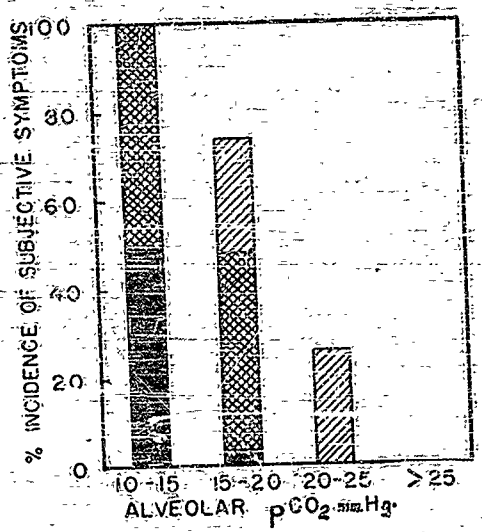


Fig. 3. Incidence of subjective symptoms at various ranges of alveolar carbon dioxide tensions in subjects breathing oxygen at 30,000 feet. The height of the bar for each range indicates the percentage of subjects within the indicated range who reported symptoms. The shading of the bars has the following meaning: solid—severe symptoms; cross-hatched—moderate symptoms; single-hatched—mild symptoms. The number of cases in each range was 10-15 mm., 2 cases; 15-20 mm., 27 cases; 20-25 mm., 23 cases.

OBSERVATIONS ON SUBJECTIVE SYMPTOMS DURING PERFORMANCE TEST FLIGHTS

During the performance test flights the subjects were requested to record their subjective sensations of acapnia, especially tingling, as completely as possible. We have classified these symptoms into three groups according to their severity as follows: (1) Slight, tingling local in extent, e.g., only in the extremities; (2) Moderate, tingling more extensive; (3) Severe, tingling or tightness over all or most of body, verging on tetany.

greater in the lower of these two ranges. The subjective symptoms, therefore, show the same general trend as the performance tests.

DISCUSSION

As far as we know, the present series of experiments are the first to attempt a quantitative evaluation of the effects of varying degrees of acapnia on performance. Gellhorn and Spiesman (1935) have described effects of brief periods of hyperventilation on hearing, after images and caloric nystagmus, but no measurements of the pCO_2 of alveolar air or the blood were made.

There are of course cases in which acapnia is the cause of collapse of aviators as has been recently pointed out by Hinshaw, Rushmer and Boothby (1943) but in these cases the alveolar pCO_2 was presumably less than 25 mm. Hg. Our results indicate that for periods of a half hour or an hour overventilation down to this level can be carried out with impunity.

According to some recent experiments of ours which will be reported later, the effects of acapnia and anoxia are largely additive. If this conclusion is correct, a gain in pO_2 in exchange for a loss of pCO_2 will be advantageous under certain conditions but disadvantageous under others. This will depend upon the particular range of tensions of O_2 or CO_2, upon the particular test used as a criterion, and upon the individual. In general, a loss of pCO_2 for a gain in pO_2 will be a disadvantage (1) in ranges of tension where acapnia is severe and anoxia mild (2) in individuals who are particularly sensitive to acapnia and insensitive to anoxia and (3) with tests like the steadiness test which are particularly affected by acapnia and relatively less affected by anoxia. A complete elaboration of this picture for the "average" man must await the accumulation of a large amount of data.

SUMMARY

The effects of hypocapnia on performance were measured by subjective sensations and by four different tests as follows: hand steadiness, choice reaction time, multiplication time, and contrast discrimination. The tests were run at 30,000 ft. simulated altitude breathing oxygen through a pneumolator by which the ventilation volume could be set at any desired level and maintained for long periods. The alveolar carbon dioxide tension was determined at each level where tests were made. All the tests indicated that the performance was very little affected until the alveolar carbon dioxide tension fell below 25 mm. Hg. With further fall of tension the performance became progressively worse.

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Survival Differences Breathing Air and Oxygen at Equivalent Altitudes.*†

HERMANN RAHN AND ARTHUR B. OTIS.

It can be shown on theoretical grounds[1] that when equivalent altitudes are chosen where the pO_2 of the inspired gases are identical breathing air and breathing 100% oxygen the resultant *alveolar* pO_2 in the lung are never the same unless the respiratory quotient is equal to unity. For example, if the alveolar pCO_2 is 40 mm Hg and the R.Q. = .8, the alveolar pO_2 is 8 mm lower breathing air than breathing 100% oxygen. Under the same conditions but with the R.Q. = 1.0 the alveolar pO_2 is the same. When the R.Q. is greater than 1.0 the alv. pO_2 is larger breathing air than breathing 100% oxygen. Thus at equivalent inspired O_2 tension altitudes the relative advantage or disadvantage of breathing air as compared to 100% oxygen is a function of the R.Q. This phenomenon has been referred to as the *R.Q. Effect* or *Nitrogen Dilution Effect* (the latter applies more specifically to conditions of R.Q. greater than unity). Acute exposure to low oxygen concentration induces hyperventilation which raises temporarily the respiratory quotient above 1.0. As long as the quotient remains above 1.0 it would be preferable to breath air rather than 100% oxygen at equivalent inspired O_2 pressures. Theoretically an advantage of only a few mm in alveolar pO_2 pressure is expected, but since in very low hypoxic environments a few mm pO_2 spell the difference between consciousness and unconsciousness it was felt that this nitrogen dilution effect might be demonstrable.

Method. Mice were conditioned to sit on a horizontal bar of ½" diameter suspended about 8 cm above the base of a large desiccator. The bottom was provided with a metal grid which electrically shocked the animal whenever it left the bar. Mice are very readily conditioned to this procedure and will immediately jump on the bar even when no current is sent through the grid. *Unconsciousness* was designated as that state where mice were no longer able to maintain themselves on the bar. This criterion has proven to be a very satisfactory index. The oxygen pressure was reduced by evacuating the desiccator by a pump. The rates of ascent on air and 100% O_2 had to be very accurately controlled so that the rates of change of the inspired pO_2 (B.T.P.S.) were identical in the two runs. Thus the timing of air runs started at ground level where the inspired pO_2 was .209 x (B-47). In the 100% O_2 runs the desiccator was first thoroughly flushed with oxygen for several minutes. This was followed by a slow ascent to an altitude of approximately 32900 ft. to allow for denitrogenation. The timing of the pure oxygen runs was started at this altitude where the inspired pO_2 (equal to B-47) was the same as at ground level.

Usually 6 mice were "taken up" at one time and the inspired pO_2 was calculated from the altitude at which unconsciousness set in. The air temperature on all runs was kept between 22.9 and 24.1°C.

Since the N_2 dilution or R.Q. effect is a transient affair depending upon the degree of hyperventilation and the magnitude of the CO_2 reserve of the blood and tissues, the rate of ascent was varied as indicated in Table I. The rates of ascent so listed are based upon 100% oxygen runs which started at 32900 ft. The ascents on air were adjusted in such a

* This work was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Rochester. For continued support since 1946, we are indebted to a contract with the Air Materiel Command, Wright Field, Dayton, Ohio.

† The authors are greatly indebted to Mr. James Holmes for his technical assistance.

[1] Fenn, W. O., Rahn, H., and Otis, A. B., *Am. J. Physiol.*, 1946, **146**, 637.

TABLE I.

Oxygen Tension (B.T.P.S. —37°C) of the Inspired Gas at Which Mice Developed Unconsciousness Breathing Air and Pure Oxygen.

Series	Rate of ascent 10^3 ft./min.	pO_2 on 100% O_2 mmHg	S.D. mmHg	n	pO_2 on air mmHg	S.D. mmHg	n	Δ mmHg	S.E.D. mmHg
I	0.5	23.3	12.2	23	24.6	1.7	23	—1.3	2.40
II	2.	41.7	7.6	33	32.5	5.6	35	9.2	1.63
III	4.	39.8	7.0	23	31.0	3.5	33	8.8	1.45
IV	16.	40.8	6.5	22	31.7	3.7	22	9.1	1.60

fashion that the inspired pO_2 at any time was equal to that of the O_2 runs.

Results and Discussion. Four different rates of ascent were tried. In Series I it took on the average 42 minutes to reach the unconsciousness level and there was no significant difference between the two runs. It might be argued that during this long interval the N_2 dilution effect was nearly over (the CO_2 reserves used up) as has been found for altitudes of 18-22000 in man.[2] Had a still slower rate of ascent been used where the R.Q. had time to return to its true metabolic value the tolerance on O_2 should have been better than on air. In such a case a N_2 concentration effect would have obtained.

In Series 2, 3 and 4 the rate of ascent was increased so that unconsciousness was reached after 6, 3 and 1 minutes respectively. It was felt that some of these ascent rates should catch the maximum N_2 dilution effect. This one would expect to be maximal at the beginning of hypoxic ventilation. It can be seen that all 3 rates gave approximately the same difference in pO_2 level at which unconsciousness was produced. All these differences are highly significant as indicated by the standard error of the differences between the means as shown in the last column of Table I. The pO_2 difference can also be expressed in terms of altitude. In other words, if the N_2 dilution effect were not present in the air runs then the unconscious level would have been reached at an altitude of 28500 ft. (inspired pO_2 of 41) instead of 33000 ft. (inspired pO_2 of 31).

It should be pointed out that another factor might enter into the discrepancy of these two runs. That is the possible occurrence of aeroembolism in the oxygen runs which by itself may contribute to the lower pO_2 threshold. Furthermore, the criterion of the inspired pO_2 at B.T.P.S. ($T = 37°C$) is probably not strictly true at very low hypoxic levels when the metabolism and the body temperature sink rapidly in these small animals. This temperature drop would increase the pO_2 tension. However, this should affect both series and if effective at all would favor the 100% O_2 animals.

Summary. Mice were exposed progressively to equivalent degrees of hypoxia breathing air and breathing 100% O_2. The inspired pO_2 level at which unconsciousness set in was found to be significantly lower when air was breathed than when 100% oxygen was breathed provided the rate of ascent was 2×10^3 ft/min or greater. This advantage of air over oxygen is attributed to the transient "N_2 dilution" or R.Q. effect.

[2] Rahn, H., and Otis, A. B., *Am. J. Physiol.*, 1947, **150**, 202.

Effects of Adding Carbon Dioxide to Inspired Oxygen on Tolerance to High Altitudes.*

A. B. Otis, H. Rahn, and L. E. Chadwick.

When CO_2 is added to the inspired air at altitudes around 20,000 feet or to low oxygen mixtures, there is an improvement in the physiological condition which is due to an increase in the alveolar pO_2.[1-4] There is no general agreement, however, on the question

* Work done under contract recommended by Committee on Medical Research between the Office of Scientific Research and Development and the University of Rochester, and under contract with Air Materiel Command, Wright Field.

1 Fenn, W. O., Rahn, H., and Otis, A. B., *Am. J. Physiol.*, 1946, **146**, 637.

2 Rahn, H., and Otis, A. B., *Am. J. Physiol.*, 1947, **150**, 202.

3 Gray, J. S., A.A.F. School of Aviation Medicine, Randolph Field, Project Report 310, August, 1944.

4 Gibbs, E. A., Gibbs, E. L., Lennox, W. G., and Nims, L. F., *J. Av. Med.*, 1943, **14**, 250.

of whether any advantage is gained by adding CO_2 to pure oxygen at high altitudes. For example, Humm *et al.*[5] and Garasenko[6] seem to find favorable effects. On the other hand, Johnson *et al.*[7] and Himwich *et al.*[8] are unable to find any benefit. The data reported below confirm the latter point of view.

Experiments on Mice. Four series of mice maintained on a stock diet were exposed in an evacuated chamber (a vacuum desiccator) to simulated altitudes in excess of 40,000 feet in various gas mixtures. Before the experiments were begun, the mice were conditioned individually to sit on a horizontal cross bar, ½ inch in diameter, which extended across the experimental chamber 3 inches above the floor. The latter consisted of a double metal grill which was connected to the secondary coil of an inductorium. When a mouse was on the grill, the operator could shock him at will by depressing a key in the primary circuit. After a few trials, the mice learned to seek safety on the cross bar, and would voluntarily take position there whenever they were put into the chamber. It was thus possible to use as an end point in the experiments the altitude at which a mouse was no longer able to maintain himself on the cross bar. In this way there was established a fairly definite criterion which did not depend on the judgment of the experimenter or place too great a strain on the endurance of the mice. After proper conditioning each mouse was exposed to altitude during a number of runs in each of the several gas mixtures.

The procedure was varied in the 4 series, as follows:

Series A. Flushout with 100% oxygen at ground level for 3 minutes; ascent to 30,000 feet in 1½ min.; flushout with experimental mixture for 5 min.

Ascent to 40,000 feet in ½ min.; stay 5 min.

Further ascent in 2000-foot stages, with 5 min. at each altitude, until ceiling was reached.

Temperature varied from 22-25°C.

Three mixtures were used: 100% oxygen (April 29 to May 5), 21.7% CO_2 in O_2 (May 8 to May 20); 20% N in O_2 (May 28 to June 13).

Series B. Flushout with 100% oxygen at ground level for 2 min.; ascent to 30,000 feet in 1½ min.; flushout with test mixture for 3 min.; continuous ascent to ceiling altitude at rate of *ca.* 6,000 ft. per min.; run in constant temperature room at 20-21°C. Three mixtures were used: 100% O_2, and 21.7% CO_2 in oxygen, on alternate days between July 10 and July 28; 10.5% CO_2 in oxygen (August 8 to August 15).

Series C. Procedure as in Series B, except that the chamber was flushed out with the test mixture at 30,000 ft. for 10 min. Two mixtures were used: 10.5% CO_2 in oxygen, and 100% oxygen, on alternate days between August 15 and August 28.

Series D. Same procedure as in Series A, except that temperature was between 20-21°C. Two mixtures were used in random succession: 10.5% CO_2 in oxygen and 100% oxygen.

In a given series, the same mice were used for all the different conditions tested. Some mice were used in more than one series. Each mouse was exposed no oftener than once a day, and usually less frequently. Only one mouse was tested in each run.

The volume of the experimental chamber was approximately 5 liters. Gas flow through the chamber was continuous whenever the altitude was stationary, and amounted to about 9 liters per minute at ground level, 2.5 liters (measured at 760 mm Hg) at 30,000 feet, 1.5 liters (at 760 mm Hg) at 40,000 feet, and 1.0 liter (at 760 mm Hg) at 50,000 feet. Inflow of gas was stopped in order to make an ascent. Altitudes were read with a mercury manometer. In the later experiments, the circuit was checked frequently for leaks, which were found to be negligible.

[5] Humm, F. D., Liberman, A. M., and Nims, L. F., C.M.R. Report No. 335, July 18, 1944.

[6] Garasenko, V. M., *Am. Rev. Sov. Med.*, 1945, 2, 119.

[7] Johnson, A. E., Eckman, M., Rumsey, C., and Barach, A. L., *J. Av. Med.*, 1942, **13**, 130.

[8] Himwich, H., Fazekas, J., Herrlich, H., Johnson, A. E., and Barach, A. L., *J. Av. Med.*, 1942, **13**, 177.

TABLE I.

Series	Gas mixture	Mean ceiling altitude, 10^3 ft.	Standard deviation, 10^3 ft.	S.D. of mean, 10^3 ft.	No. of mouse runs	No. of mice
A	100% O_2	50.3	2.1	.33	41	6
	21.7% CO_2	50.9	2.4	.39	38	6
	20% N_2	49.5	2.1	.36	35	6
B	100% O_2	48.6	1.3	.19	50	15
	10.5% CO_2	47.4	1.6	.24	45	15
	21.7% CO_2	46.8	1.6	.22	52	15
C	100% O_2	48.6	1.3	.24	28	15
	10.5% CO_2	48.4	1.1	.19	29	15
D	100% O_2	53.4	2.5	.43	34	11
	10.5% CO_2	51.3	2.5	.42	36	11

TABLE II.

Summary of Measurements on Human Subjects Breathing 100% O_2 and 90% O_2-10% CO_2 at 40,000 Feet.

	Min. vol. liters/min. B.T.P.S.		Oximeter, % saturation		Alveolar pCO_2, mm Hg	
Subject	100% O_2	90% O_2-10% CO_2	100% O_2	90% O_2-10% CO_2	100% O_2	90% O_2-10% CO_2
R	14.9	18.2	92.6	91.8	31.9	34.9
S	17.5	21.1	90.6	90.5	37.2	38.1
H	10.3	12.2	92.1	91.8	37.8	37.8
Mean	14.2	17.2	91.8	91.4	35.6	36.9
Δ		+3.0		−0.4		+1.3

Results. Average results for each series are presented in Table I. In none of the series was there any significant increase in altitude ceiling as a result of addition of carbon dioxide to the experimental mixture.

In series A, the substitution of 20% nitrogen for oxygen resulted in a slight but probably real decrease in ceiling.

In series B, the performance was definitely worse in both carbon dioxide mixtures than in 100% oxygen, and probably worse in the higher than in the lower concentration of carbon dioxide. On the other hand, in series C where the mice spent 10 minutes at 30,000 feet in the experimental mixture, instead of only 3 minutes as in series B, approximately the same altitudes were reached in 10.5% carbon dioxide as in pure oxygen. In series D, which resembles series A in that 5-minute stops were made at 2,000-foot intervals above 40,000 feet, performance was definitely better in 100% oxygen.

In view of these findings, it may be concluded definitely that mice gain no benefit, in terms of altitude ceiling, from the substitution of carbon dioxide for oxygen with the patterns employed in these experiments. In some cases, a definite harmful effect (decreased ceiling with added carbon dioxide) has been demonstrated.

Differences in the average ceiling altitude attained in a given gas mixture in the several series may be due to:

(1) Differences in altitude tolerance of individual mice; (2) Slight temperature difference between series A and the other series; (3) Variations in the adaptation of circulatory and other mechanisms resulting from different patterns (rates) of ascent.[9]

Experiments on Human Subjects. Each of 3 male subjects was taken to a simulated altitude of 40,000 feet wearing an ear oximeter (Millikan compensated circuit) and inspiring 100% oxygen through a gas meter. Measurements of the ventilation and oximeter readings were made during a 15-minute

[9] Hiestand, W. A., and Miller, H. R., *Am. J. Physiol.*, 1944, **142**, 310.

period, and near the end of this interval an end-expiratory alveolar sample was secured. The inspired gas was then changed to a mixture of 10% CO_2 and 90% O_2, and measurements were continued for another 15 minutes at the end of which another alveolar sample was taken.

Results are summarized in Table II. Substitution of the CO_2-O_2 mixture for pure oxygen produced a rise of 1.3 mm in the alveolar pCO_2 (with lowering of the alveolar pO_2 by the same amount) and a drop of 0.4% in the saturation as determined from the oximeter. The change in % saturation is within the error of the instrument, but the expected change for the change in alveolar gas tensions is about 1%. The minute volume of ventilation was increased by 3 liters per minute or about 21%. These data indicate that no favorable physiological changes occurred from the addition of 10% CO_2 (9.4 mm) to the inspired gas at 40,000 feet. One cannot argue from this that it would not be advantageous to add CO_2 under some conditions, but it must be kept in mind that any rise in alveolar pCO_2 is always accompanied by an equivalent drop in alveolar pO_2 when nitrogen is absent. Probably the only condition in which substitution of a CO_2-O_2 mixture for pure O_2 might be advantageous is that of severe hypocapnia accompanied by a relatively mild hypoxia. In such a case the improvement due to the decreased hypocapnia might be greater than the impairment due to the increased anoxia.[10]

Summary. 1. The addition of 10.5% or 21.7% carbon dioxide to oxygen does not improve the altitude ceiling of mice.

2. Mice taken to altitude in 100% oxygen, with continuous ascent from 30,000 feet at a rate of about 6,000 feet per minute, collapse at a lower ceiling than mice which ascend from 40,000 feet in 2,000-foot steps with 5-minute stops at each stage.

3. In experiments on human subjects no favorable physiological effects were observed when 10% CO_2 was added to the inspired oxygen at 40,000 ft.

[10] Otis, A. B., Rahn, H., Epstein, M. A., and Fenn, W. O., *Am. J. Physiol.*, 1946, **146**, 207.

Corneo-retinal Potential in Anoxia and Acapnia

W. O. FENN, R. GALAMBOS, A. B. OTIS AND H. RAHN

THE CORNEO-RETINAL POTENTIAL was first used for the recording of eye movements in man by Fenn and Hursh (1). They placed electrodes just lateral to the eyes on each side of the head and recorded with a string galvanometer the potentials developed when the eyes were moved right or left. The results showed that the deflection obtained on the record was directly proportional to the sine of the angle of deviation of the eyes. The same phenomenon can now be used in reverse, i.e., by deviating the eyes right and left alternately to a constant degree and measuring the deflection of the galvanometer an estimate can be made of any changes in the corneo-retinal potential which may result from changes in the condition of the subject. It occurred to us that this potential might show characteristic changes in anoxia and acapnia and might even be useful as a physiological measure of the effect of low O_2 or low CO_2 on the body.

METHOD

Electrodes were of the type used for brain-wave recording and consisted of a shallow cup attached to the skin with collodion. Through a hole in the cup, the underlying space was filled with electrode jelly. One of these electrodes was attached to each side of the head just lateral to the eyes. To provide points of fixation for the eyes, a wooden T was prepared, the top of which was 50 cm. in length and the upright 26 cm. In taking a record, the T was held horizontally with the base of the upright against the front of the oxygen mask, and the eyes were fixated alternately on two nails fixed at either end of the crossbar. The angle of deviation of the eyes was, therefore, about 45° to each side of the center. The string was used at a sensitivity of about 3 cm./m.v. A calibration deflection with the eyes fixated in the midline was recorded just before each record of eye movement so that all movements could be expressed in millivolts.

RESULTS

Anoxia. These experiments were begun with the idea that the corneo-retinal potential (CRP) might vary with anoxia. To test this, 18 experiments were tried in which the CRP was recorded during decompression to 18, 20 or 23 thousand feet or during the inhalation of 9 per cent O_2 in N_2 at ground level.

The results of a preliminary series of 6 such experiments are shown in table 1. In this series only one record was taken at each altitude and the figures are not very reliable. On the average, however, there was a 16 per cent increase in the CRP with only one small decrease recorded.

TABLE 1. PRELIMINARY MEASUREMENTS OF THE EFFECT OF ANOXIA ON THE CORNEO-RETINAL POTENTIAL (CRP) (ONLY ONE RECORD FOR EACH FIGURE)

SUBJECT	DATE	ALTITUDE 10^3 FT.	INSPIRED GAS	NORMAL CRP.	MAXIMUM CRP.	INCREASE
				m. v.	m. v.	%
M. A. E.	1/3	20	O_2	.36	.465	29
M. A. E.	1/3	15	air	.48	.56	17
L. E. C.	1/4	18	air	.85	.925	9
H. R.	1/5	18	air	.427	.441	4
L. E. C.	1/5	18	air	.523	.567	8
V. G. S.	1/5	(a) 15	air	.40	.56	31
		(b) 40	O_2	.40	.59	25
Average				.49	.57	16

TABLE 2. EFFECT OF ANOXIA AND ACAPNIA ON THE CORNEO-RETINAL POTENTIAL

SUBJECT	DATE	ALTITUDE 10^3 FT.	INSPIRED GAS	NORMAL CRP.	MAXIMUM CRP.	INCREASE
Anoxia						
				m. v.	m. v.	%
C. G. B.	1/20	0	9%O_2	.83	1.44	74
C. G. B.	1/25	0	9%O_2	.83	1.37	65
C. G. B.	1/27	20	air	.70	1.19	70
C. G. B.	3/3	0	9%O_2	.95	1.14	20
G. G. B.	3/11	(a) 18	air	1.09	1.34	23
		(b) 21	air	1.09	1.86	71
J. A. F.	1/25	(a) 20	air	1.03	1.14	11
		(b) 23	air	1.03	1.55	50
J. A. F.	2/10	18	air	.96	.99	1
M. A. E.	1/27	20	air	1.10	1.31	19
M. A. E.	2/10	18	air	.87	.81	−7
M. A. E.	1/22	0	9%O_2	.77	.74	−4
V. G. S.	2/10	18	air	.74	.73	−1
R. G.	3/11	18	air	1.09	1.05	−4

For each CRP measurement 3 or more records were measured and averaged. Except for subject *C. G. B.* and for *J. A. F.* at 23,000 feet, the increases in CRP are not impressive.

Subsequently, the electrodes were improved and tested for constancy in control experiments and records were taken at frequent intervals throughout the experiments. The results of 12 such experiments are given in table 2 on 5 different subjects. In this series, large increases in CRP averaging 54 per cent were regularly observed in one subject (*C. G. B.*) but only 2 of the

other 7 experiments showed any appreciable change. From this, it is evident that subjects vary markedly in their responses but anoxia has no effect except in a few cases. It seemed possible that these results might depend upon the

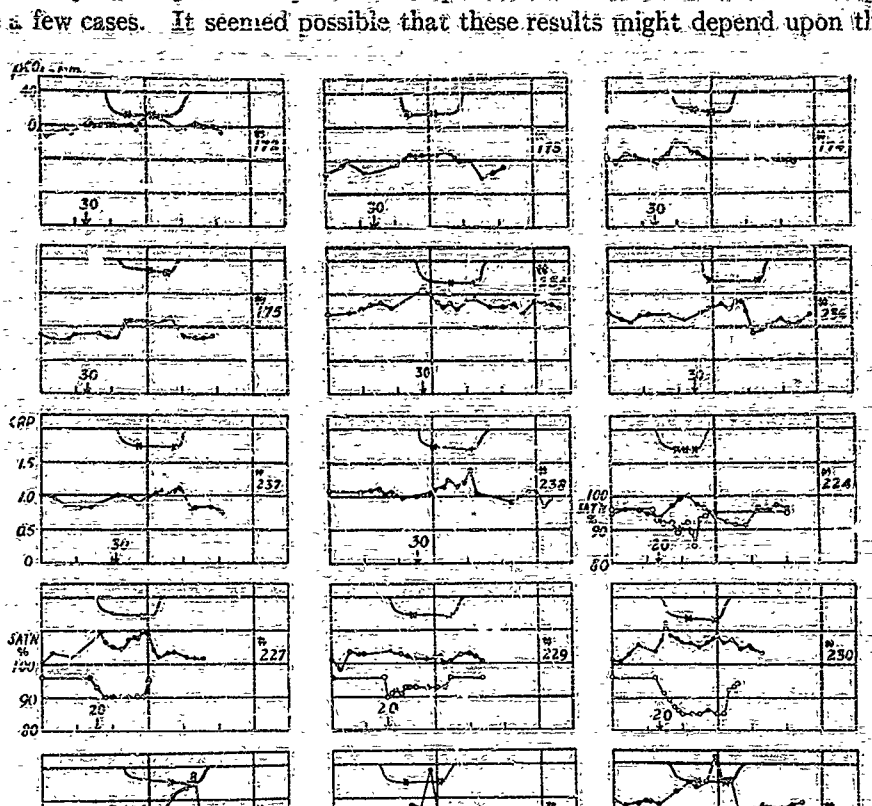

Fig. 1. CORNEO-RETINAL POTENTIALS before, during, and after hyperventilation on the pneumolator. Time of arrival at altitude is indicated by an arrow in each chart. The altitude in thousands of feet was 30 or 20 as indicated by the figure over the arrow. The upper curve in each chart (crosses) is the alveolar CO_2 tension, the middle curve (dots), the corneo-retinal potential, and the lower curve (open circles), the oximeter readings. In general the CRP goes up when the pCO_2 goes down. The time of descent is indicated by the rise of the pCO_2 curve. Groups of points were averaged together for the statistical study of table 5.

varying degrees of hyperventilation in different subjects under anoxic conditions. Indeed, all of the effects observed might be due to the acapnia which inevitably accompanies anoxia in varying degrees. Another series of experiments was, therefore, carried out. The results are shown in figure 1[2]. Two kinds of experiments are included: 1) acapnia alone and 2) acapnia with anoxia.

[2] Complete data of these experiments are given in table 3 of Part VII of our original report No. 410 to Committee on Aviation Medicine of the O.S.R.D. December 18, 1944 obtainable from the National Research Council, Washington, D.C.

For the acapnia alone, the subjects were taken to a simulated altitude of 30,000 feet breathing O_2. Records of CRP were taken at ground level and at altitude without hyperventilation. Then O_2 was taken through the G.E. pneumolator set for a high ventilation rate and alveolar samples were taken at intervals in order to follow the pCO_2 along with the CRP. After 20 to 30 minutes of hyperventilation, the chamber was brought back to ground level and recovery was followed breathing air for 20 to 30 minutes. The first 8 experiments in figure 1 (nos. 172–238) were of this type.

TABLE 3. ADDITIONAL EXPERIMENTS ON THE EFFECTS OF ACAPNIA WITHOUT ANOXIA

FLIGHT	SUBJECT	ALTITUDE	ALVEOLAR pCO_2	MEAN CRP	MEAN Δ CRP	DURATION	NO. OF TESTS
			mm. Hg	*m.v.*	*m.v.*	*min.*	
2/13	*R. G.*	GL	(40)	.90			3
		30 on O_2	24	.99	+.09	16	3
		30	21	1.00	+.10	32	2
		GL					
2/20	*M. E.*	GL	(40)	.98			3
		18 on O_2	20	1.12	+.14	17	2
		18	15	1.16	+.18	45	3
		GL	(40)	1.06	+.08	10	2
2/22	*C. B.*	GL	(40)	.93			3
		30 on O_2	18	1.25	+.32	10	3
		30	14	1.19	+.26	45	4
		GL	(40)	.87	−.06	20	1
2/24	*C. B.*	GL	(40)	.91		20	4
		GL	27	1.06	+.15	15	7
		GL	20	1.28	+.37	55	6
		GL	(40)	1.05	+.14	20	2
2/29	*W. F.*	GL	(40)	1.46			4
		GL	18.5	1.52	+.06	15	3
		GL	17	1.58	+.12	32	5
		GL	16	1.61	+.15	60	5
			(40)	1.58	+.12	28	1

For anoxic acapnia a similar procedure was followed except that the subject was taken to 20,000 feet breathing air through the pneumolator,[3] and no records were taken at altitude without hyperventilation. In these experiments the arterial saturation was also followed with a Millikan-Coleman oximeter. The next 7 experiments of figure 1 (224–233) were of this type. All these 15 experiments are plotted in figure 1 to show the time course of the changes in pCO_2, CRP, and saturation.

[3] The pneumolator is an apparatus built by the General Electric X-Ray Corporation which facilitates hyperventilation by providing positive pressure during inspiration and ambient pressure during expiration.

The 5 additional experiments in table 3 are similar to the first type in that they involved acapnia alone, but they differ in some details of procedure. Two of these experiments were done at ground level in air and one of them at 18,000 feet instead of 30,000 feet on O_2, but in all cases the pneumolator was used and there was no anoxia. In the statistical analysis these 5 experiments have not been treated as part of the series.

All the experiments in figure 1 and table 3 are represented in a mass plot in figure 2. Experiments at 20,000 feet with anoxia are plotted as solid circles while acapnia points without anoxia are plotted as empty circles. It is evident that all the points with or without anoxia fall within the same range showing an

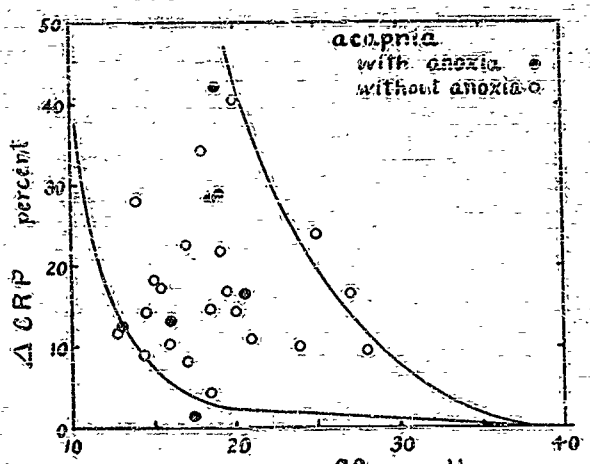

FIG. 2. PERCENTAGE CHANGES in the corneo-retinal potential (ordinates) at different levels of alveolar CO_2 tension (abscissae) as compared to the ground level value at about 40 mm. pCO_2. Points with anoxia were run at 18,000 ft. breathing air and do not differ significantly from similar points without anoxia (open circles). The lines suggest the probable family of curves represented by the points.

increase in CRP with lowering of the pCO_2 and none of the experiments indicates a fall in CRP. In the latter respect they are all surprisingly uniform although the scatter is very large.

Table 4 shows a comparison of acapnia with anoxic acapnia for 8 different subjects. The percentage increase in CRP is given for each condition together with the corresponding alveolar pCO_2. Inspection shows that for any one subject the pCO_2 values are about the same for the two conditions (being, if anything, higher in anoxia) while the CRP increases are only a little higher in anoxic acapnia than in pure acapnia. It could hardly be said from this table that anoxia per se had any significant effect on the CRP.

A similar conclusion is reached from the summary given in table 5 of the experiments of figure 1. The results of the 8 pure acapnia flights and the 7 anoxic acapnia flights are averaged separately. The rise in CRP is 0.14 ± .013 m.v. without anoxia and .24 ± .035 m.v. with anoxia. The probability that the difference between these two figures is due to chance is 14 out of 100. It can be concluded that in the subjects represented in figure 1 the effect of anoxia is small compared to the effect of acapnia. In *C.G.B.*, however, the effect of anoxia accompanied only by a normal amount of decrease in the pCO_2 gives a

much larger rise in CRP than does a considerably greater acapnia without any anoxia and this suggests that further study might establish a definite small effect due to anoxia in all subjects.

The individual experiments plotted in figure 1 show the general course of the changes which were recorded. Only the 20,000-ft. flights include a curve

TABLE 4. COMPARISON OF THE EFFECTS OF ACAPNIA AND ANOXIC ACAPNIA ON THE CORNEO-RETINAL POTENTIAL (CRP) USING IDENTICAL SUBJECTS

SUBJECT	ACAPNIA WITH O_2		ANOXIC ACAPNIA	
	Alveolar pCO_2	Increase in CRP	Alveolar pCO_2	Increase in CRP
	mm. Hg	%	*mm. Hg*	%
W. O. F.	12.8	11.6	13.1	12.1
H. R.	17.0	22.6	16.0	13.3
M. A. E.	25.0	23.1	26.3	22.4
R. W. S.	14.4	9.1	20.0	24.2
J. MCW.	18.6	14.7	18.0	28.2
I. H.	16.9	8.2	17.5	1.4
M. H.	15.5	17.3	18.5	28.2
C. G. B.	18.0	34.4	(25.7)	52.0
Average	17.3	17.7	18.6	22.7

TABLE 5. AVERAGES OF CORNEO-RETINAL POTENTIALS (CRP) WITH PROBABLE ERRORS (PE) AT ALTITUDE AND GROUND LEVEL (GL) AS A FUNCTION OF ALVEOLAR pCO_2

ALTITUDE IN 1000 FEET	AVERAGE pCO_2	MEAN CRP	PE OF MEAN CRP	MEAN Δ CRP	NO. OF TESTS	NO. OF FLIGHTS
	mm. Hg	*m. v.*	*m. v.*	*m. v.*		
GL	(40.0)	1.06	.04		43	8
30	35.0	1.09	.12	+0.05	11	4
30	17.2	1.20	.04	+0.14	61	8
GL	(40.0)	1.04	.04	+0.02	43	8
GL	(40.0)	1.10	.04		32	7
20	18.3	1.34	.05	+0.24	58	7
GL	(40.0)	1.12	.03	+0.02	46	7

The percentage incidence of slight, moderate and severe acapnia was 12, 50 and 39 respectively at 30,000 ft. and 15, 71 and 14 respectively at 20,000 ft. Oxygen was inhaled at 30,000 and air at 20,000 ft. All the potentials are given in millivolts. Figures in ( ) are assumed values. Differences in CRP are differences from original GL value. These values for Δ CRP are not always equal to the differences in the mean CRP values because the latter referred to different numbers of flights. Averages obtained from the data of fig. 1.

for arterial saturation. The pCO_2 curves are represented as dropping promptly to a new level when hyperventilation began. This is justified by other experiments in which more frequent analyses of alveolar air were made. The CRP curves show the magnitude of the variations met with and show how the CRP often rises to a peak and then falls even before the pCO_2 begins to rise, as if some process of adaptation had occurred. This suggests that the CRP is not a direct function of pCO_2, but depends upon a number of factors within the organism

and is, therefore, subject to much variation between individuals. For the statictical study of these data (table 5) representative groups of points were averaged together.

These potentials are not significantly modified by light conditions. In one experiment on *C. G. B.* the values obtained during a preliminary period of light adaptation were reproduced throughout a subsequent 50-minute period of dark adaptation and during 5 minutes of light adaptation thereafter. This is in agreement with previous information for if the eyes are deviated far to one side in the dark and held stationary in that position while a bright light is turned on, the record of the string shows no deflection.

One observation made during the course of these experiments confirms the reports of others, and that is a loss in the precision of ocular movements. McFarland *et al.* (2, 3) have reported such a finding with anoxia—they also found deterioration of eye movements in reading under such conditions. We have found that the movements became generally slower with acapnia and often the records were very erratic and difficult to measure.

Gross changes in skin (and possibly also retinal) circulation are ineffective in changing normal potentials. One subject, *C.G.B.*, breathing room air received .5 cc. (10 units) pituitrin subcutaneously; marked vaso-constriction (pallor) ensued, but the eye potentials did not vary. During the course of the next half hour, 2 amyl-nitrite inhalations, each sufficient to evoke giddiness, flushing and obvious vaso-dilatation, were ineffective in changing the potentials.

As an explanation of the changes in CRP which have been reported it is natural to think first of the pH change which accompanies acapnia and, to a lesser extent, anoxia. The marked differences between individuals and the failure of the potential to remain constant at a higher level so long as the CO_2 remains low suggest that other factors must also be involved. On account of this variability, the measurement of the corneo-retinal potential can hardly be recommended as a measure of acapnia.

SUMMARY

The corneo-retinal potential is increased about 20 per cent by acapnia with an alveolar pCO_2 of about 18 mm. Anoxia also increases the potential, but this is largely due to the overventilation and acapnia which accompanies it. In some individuals, however, anoxia itself seems to increase the potentials even more than acapnia.

We are indebted for collaboration in these experiments to Dr. L. E. Chadwick, Dr. M. A. Epstein and Dr. C. G. Bly and to various members of Civilian Public Service Unit No. 115-R who served as subjects for the experiments.

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A Method for the Continuous Analysis of Alveolar Air

By Hermann Rahn, Jack Mohney, Arthur B. Otis, and Wallace O. Fenn

With the technical assistance of

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THE GENERAL disadvantages of relying upon the conventional Haldane-Priestley methods for composition of alveolar gases are well known. Firstly, it requires an experienced person to deliver a sample in precisely the same fashion time after time. Secondly, it interrupts the general breathing pattern during an experiment and induces a temporary hyperventilation of 1 to 2 liters. This makes frequent sampling impossible. Thirdly, the analysis is rather time-consuming, particularly when check samples are required. Lastly, it is still debatable how closely such samples resemble the typical or average alveolar air after considering the work of Aitken and Clarke-Kennedy (1928) Roelsen (1939), and Engelhardt (1942), on the fractional analysis of expired alveolar air.

The method outlined below overcomes many of these drawbacks, but, nevertheless, does not bring us any closer to the question last posed. It establishes values which differ from those obtained by the conventional method, but allows the continuous analysis of the alveolar fraction of tidal air during normal respiration. A trained subject is not essential, since only the normal breathing from mask or mouthpiece is required.

The principle of using the last part of each normal expired tidal volume as an index of alveolar air goes back to Krogh and Lindhard (1914). Henderson and Haggard (1925) produced the first automatic device which sampled the last part of each expiration beyond the expiratory valve. The inspiratory mask pressure was used with the aid of a Muller Valve to suck the sample into the collection flask. Clarke-Kennedy and Owen (1927) improved this system with an automatic syphoning arrangement. The inspiratory pressure motivated electrically a tap valve which allowed the syphoning system to suck over the alveolar sample and stop it during expiration. Benzinger and Brauch (1934) combined this technique with the continuous gas analysis apparatus of Rein. Instead of using a syphoning bottle they activated a pump during each inspiration to draw a sample for the analyzers. Loeschke, Opitz and Schoedel (1939) modified this arrangement in such a fashion that the alveolar sample was drawn during the last phase of expiration but only after a tidal air of certain volume

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Rochester.

had been expired. This safeguarded against sampling after very shallow tidal volumes which would still be diluted with dead space air. On the other hand, it might yield unreliable results for very large expiration.

Our apparatus was quite independently evolved, but is based upon exactly the same principle. Approximately 10 c.c. of gas are removed from the last part of each expiration just beyond the expiratory check valve and are pulled through the automatic oxygen and carbon dioxide analyzers. The Pauling oxygen tensimeter is used to measure the partial pressure of oxygen, while a Cambridge thermoconductivity meter records the percentage of carbon dioxide.

DESCRIPTION OF APPARATUS

The inspiratory and expiratory flows are separated by means of check valves. The apparatus dead space must be kept as small as possible in order to insure complete flushing of dead space air with each expiration. For this reason the inspiratory port was placed at right angles to the expiratory tube. The mouthpiece later was replaced with a small B.L.B. mask so that our total dead space did not exceed 60 c.c. Upon a normal expiration the tidal air escapes through the expiratory check valve into a 300 c.c. smooth-walled rubber tube. The air just beyond the valve is now trapped and ready for sampling. During the ensuing inspiration the negative mask pressure activates a sensitive aneroid

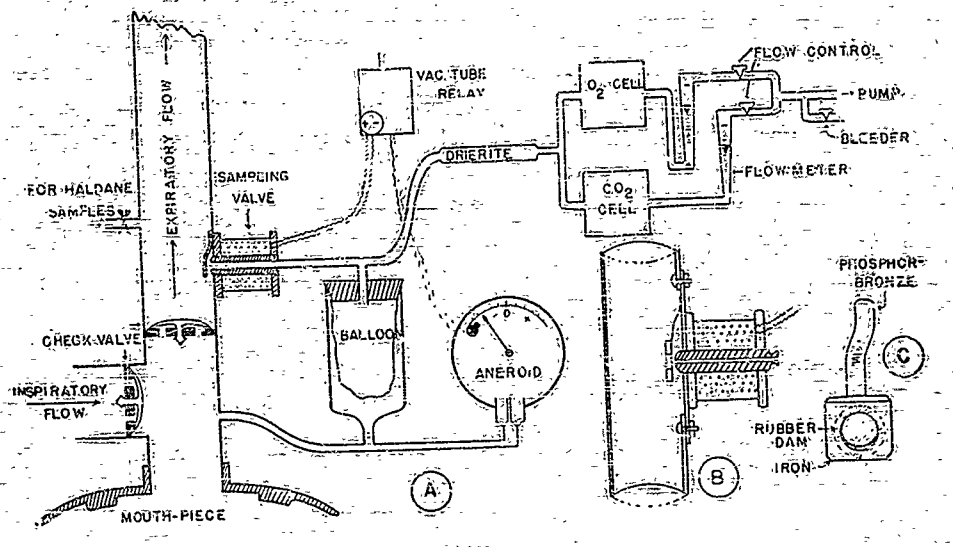

Fig. 1. (A) Schematic diagram of the apparatus for the continuous sampling and analysis of alveolar gases. For further description see text.
(B) Detailed diagram of sampling valve which is mounted on a brass plate and can be bolted to the expiratory tube.
(C) Detailed diagram of the valve head which is made of soft iron. The central hole is covered by a thin rubber dam which produces a tight fit over the nozzle when whole head is attracted to the magnet.

gauge which closes the circuit of a vacuum tube relay which in turn opens the sampler valve and allows the alveolar air sample to flow through the analyzers to the pump. Toward the end of inspiration the mask pressure approaches zero, breaking the relay circuit and closing the sampling valve. Thus no dead space air is admitted to the analyzers during the following expiration.

A small thin-walled rubber balloon is placed in series with the alveolar sample line. It collapses slowly while the valve is closed and thus prevents an interruption of the flow in the analyzers. During inspiration when the valve is open the balloon is inflated by the negative mask pressure. This is accomplished by connecting the glass housing around the balloon to the mask.

The two gas analyzers are placed in parallel so that oxygen and carbon dioxide are simultaneously analyzed. The flow of 70 c.c. per minute through each cell is controlled with help of a flow gauge while the excess capacity of the pump is adjusted by a bleeder.

Before and after each experiment the analyzers were routinely checked against known test mixtures of CO_2 and O_2. A correction curve for the oxygen tensimeter was made with six different oxygen mixtures. The values remained constant in our instrument within ±1.0 mm. Hg as long as exactly the same pressure gradient between test cell and the ambient pressure was maintained.

EXPERIMENTAL RESULTS

The principal concern has been to compare the alveolar values obtained by the continuous analyzing technique and the conventional Haldane-Priestley method. Our apparatus described above was modified in such a manner that the forced expirations as well as normal expirations could be analyzed by the oxygen and carbon dioxide meters. This was accomplished by placing a large three-way stopcock just below the expiratory check valve. After a forced expiration the stopcock was turned, thus trapping the sample either for a Haldane sample or for analysis by the meters.

Particular care was exercised in assuring a comfortable position for the subject. A steamer-deck chair was used so that the head of the subject could rest against the back. Thus the seated position was not upright but slightly inclined. The subject remained in this position for one-half to one hour during which at five- or ten-minute intervals a forced expiration was blown and analyzed either by the Haldane method or by the meters or both. These values were then compared with the continuous sampling analysis just before the forced expiration.

Care was exercised in obtaining a constant value for CO_2 and O_2 for at least three minutes before blowing the alveolar sample. The slightest disturbance in the normal respiratory rhythm, such as is induced by distraction or talking, is followed by a lowering of the alveolar CO_2 and immediately detected by the CO_2 meter. While completely at rest alveolar CO_2 values would not vary more than 3 mm. Hg for a half-hour period in many persons. Three kinds of analysis are com-

pared and will be designated by the following symbols:—

C.S. means continuous alveolar samples analyzed by the meters. Conventional alveolar samples were obtained from a forced expiration following a normal expiration. These were analyzed by the meters, Al.M. or by the Haldane gas analyzer, Al.H.

In order to ascertain the accuracy of the agreement between the Haldane gas analysis and analysis by the meters, twenty-six forced alveolar expirations were compared (Table I).

TABLE I

Differences between the means of Al.M. and Al.H. on the same gas sample.
pO_2 —0.27 ±1.28 mm. Hg
pCO_2 —0.01 ±1.07 mm. Hg

These differences are very small and indicate that for practical purposes alveolar air from forced expirations can be very quickly and accurately analyzed by automatic gas analyzing cells. This is further substantiated by the general agreement between Tables II and III. In Table II the Continuous Sample values are compared with the Al. H. values, while in Table III the Continuous Samples are compared with the Al. M. Values.

It should be pointed out that among the ten persons tested some gave consistently small differences while others gave large differences. This might indicate different mixing efficiency during normal breathing. The ratio of the CO_2 and O_2 differences is approximately 1 : 2.

The differences in pO_2 and pCO_2 between C.S. and Al.M. may be attributed to the fact that two or three seconds is required for the forcible expiration of the conventional alveolar air samples. Similar changes do occur if the breath is held for periods of five to twenty seconds and the decrement in pO_2 is about twice the increment in pCO_2 as indicated in Table III.

In a smaller number of experiments the deviations of the continuous sampling values were compared to the alveolar values delivered at the end of inspiration and also at the end of expiration. These indicate that the alveolar samples blown at the end of inspiration agree much more closely with the C. S. values. (Table IV).

TABLE II

	Mean C.S.	S.D.	Mean Al.H.	S.D.	Mean Diff.	S.D. of Mean Diff.	n
pO_2	100.6	±3.7	95.7	±6.2	+4.9	±4.08	47
pCO_2	39.3	±1.91	42.4	±2.6	—3.1	±1.67	47
R.Q.	0.831	±0.07	0.806	±0.08	+0.025	±0.022	47

TABLE III

	Mean C.S.	S.D.	Mean Al.M.	S.D.	Mean Diff.	S.D. of Mean Diff.	n
pO_2	100.0	±3.9	95.2	±5.6	+4.8	±3.03	101
pCO_2	39.1	±2.1	41.6	±2.3	—2.5	±1.26	101
R.Q.	0.816	±0.06	0.784	±0.06	+0.033	±0.036	101

TABLE IV

	pO_2	S.D.	pCO_2	S.D.	R.Q.	S.D.	n
Mean Diff. C.S. and Al. M. Expiration.....	+4.38	±3.33	—2.03	±1.18	+0.037	±0.037	24
Mean Diff. C.S. and Al. M. Inspiration.....	+2.70	±1.31	—1.13	±0.207	+0.024	±0.010	19

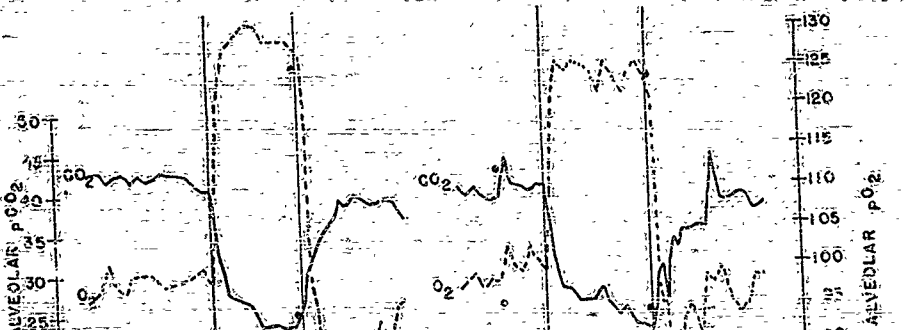

Fig. 2. Continuous alveolar gas analyzer readings taken every minute and the calculated alveolar respiratory quotient during normal breathing of two subjects H.R. and A.C. This period is followed by controlled hyperventilation (H.V.) of 20 liters per minute B.T.S. and a recovery period. Forced alveolar expirations were analyzed by the Haldane technique and are indicated by solid circles. Note the gradual drop in the alveolar CO_2 as the CO_2 stores are gradually used up with a simultaneous rise in the R.Q. Upon recovery there is a striking picture of CO_2 retention as indicated by the low R.Q. with intermittent apneic periods causing the low oxygen values. Recovery at the end of 15 minutes is far from complete in both subjects.

The application of the continuous alveolar gas analyzer to experimental procedures are illustrated in Figures 2 and 3 and legends.

SUMMARY

1. An apparatus is described for the automatic sampling and continuous analysis of alveolar air during normal respiration with an aviation mask.

2. This apparatus can also be used to analyze accurately and quickly a Haldane-Priestley sample at any time during a continuous sampling run. The reliability of such analysis was checked by the Haldane-Henderson technique of gas analysis.

3. When the values obtained by the continuous sampling system are compared to alveolar samples delivered at the end of a normal expiration they are found to average 2.5 ± 1.3 mm. Hg lower for carbon dioxide and 4.8 ± 3.0 mm. Hg higher for oxygen. This is based upon 101 comparisons in ten subjects.

4. When similar comparisons are made to alveolar samples delivered at the end of a normal inspiration the deviation is reduced by about 50 per cent.

5. The application of the continuous alveolar analysis to experiments in hyperventilation and anoxia is illustrated.

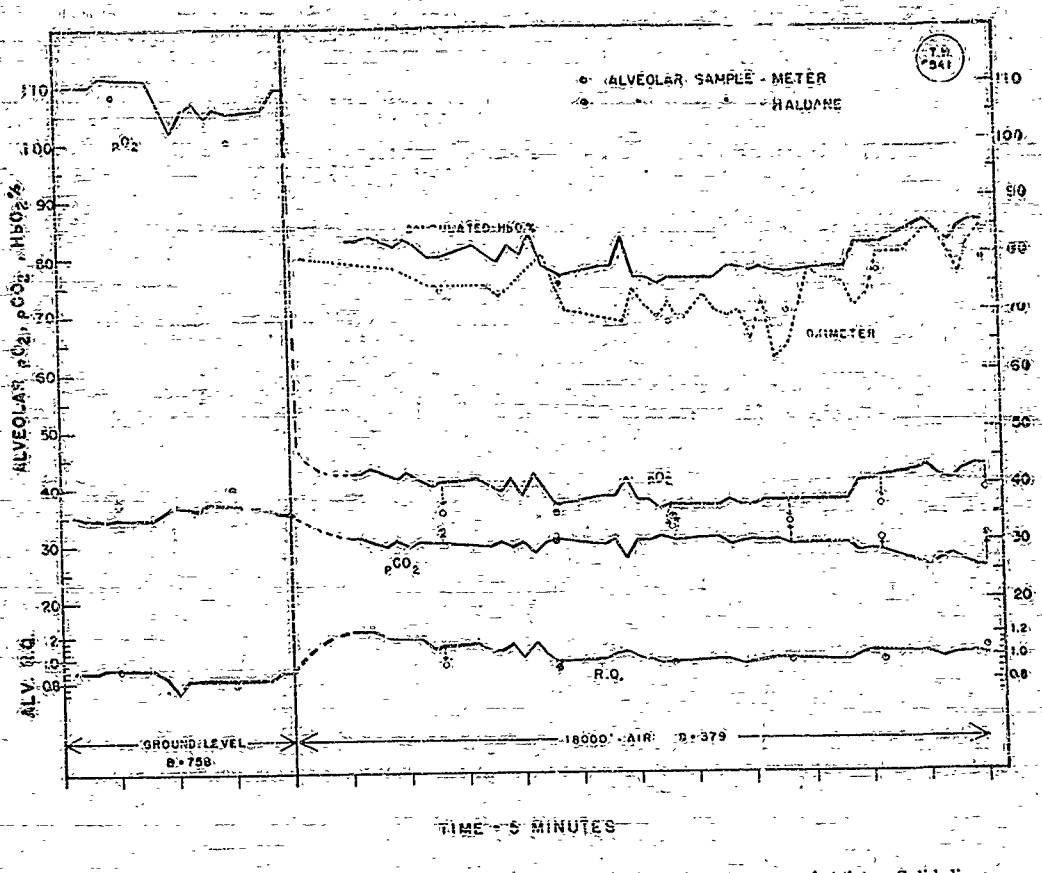

Fig. 3. One hour exposure to 18,000 feet simulated altitude in a low pressure chamber. Solid lines are the minute readings of the continuous alveolar gas analyzer and the R.Q.s and hemoglobin saturations based upon their values. The dotted line indicates the observed hemoglobin saturation as determined with the Millikan ear oximeter. Forced expirations were analyzed at approximately ten-minute intervals by the gas-analysing meters (open circles) or Haldane technique (closed circles).

It can be seen that the anoxia initially lowers the alveolar CO_2 with its concomitant rise in the respiratory quotient. After thirty to forty minutes the steady state is approached as indicated by the leveling of the R.Q. During the last ten minutes, however, another period of hyperventilation commenced reversating the former pattern to a slighter degree.

The observed oximeter readings are consistently lower than the values calculated from the continuous sampler, but agree very well when calculated from the forced expiration analysis (open circles). This would indicate that the forced expiration values are the best index of the blood gas tensions. On the other hand the continuous sampler varies by a constant fraction and thus indicates the relative trends in the respiratory gas exchange pattern.

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A Rapid Infra-Red Gas Analyzer

RICHARD C. FOWLER

A brief description of an apparatus, together with a few representative curves, is presented, suitable for measuring the composition of very small amounts of any gas having at least one near infra-red absorption band or, if measured in the presence of other gases, at least one unique absorption band. With the bolometers used, 90 percent full scale response is obtained in 0.15 seconds on a 0.5 cc sample, permitting a 0.4 cm optical path and a very nearly linear response over the range usually found in physiological concentrations and anesthesia.

IN connection with many problems in physiology, cardio-respiratory disease, anesthesia, etc., an instantaneous means for analyzing quantitatively and continuously the respired gas during the respiratory cycle is desirable. Various ingenious methods have been devised to accomplish this, each with a particular limitation. Some of these schemes, together with their outstanding features follow:

(a) The classical fractional sampling of a single expired volume of gas[1,2] lacks time or volume-composition "resolution," involves laborious chemical analysis and is not instantaneous.

(b) The thermal conductivity method again is not instantaneous, with a minimum time lag of 15 to 30 seconds,[3–6] but is commercially available in reliable form.

(c) The acoustic methods[7] are now largely in the developmental stage. They are operable for some gases including oxygen, but have not proven satisfactory for carbon dioxide and some other gases. Since some interfering gases must be removed, and because of the electrical circuit used, they will have an appreciable delay.

(d) The mass spectrometers[8,9] have a small delay, largely in the sampling device, are quite cumbersome and expensive, but have the particular advantage of multiple simultaneous analyses. There is still some question of accuracy, however, as a result of the relative velocity of gases of different characteristics.

(e) The "spectrophotometric" method, developed by Dr. Lilly[10,11] involving the continuous sampling, subsequent ionization and photoelectric measurement is relatively expensive and cumbersome and

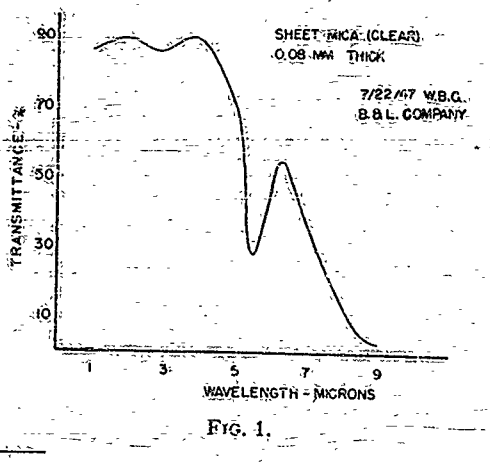

FIG. 1.

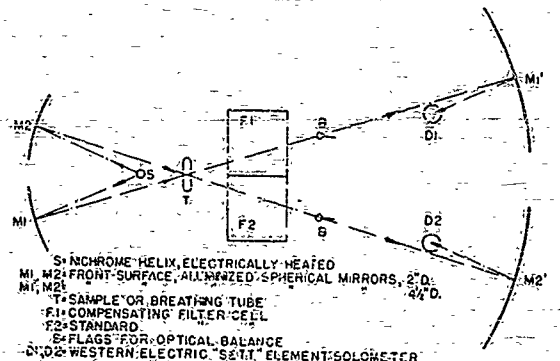

FIG. 2. Infra-red analyzer.

[1] J. S. Haldane, *Respiration* (new edition) (Yale University Press, New Haven, 1935), pp. 19.

[2] A. L. vonMuralt, *Einfuhrung in die Praktische Physiologie*, (Verlag-Julius Springer, Berlin, 1943).

[3] Gow-Mac Instrument Company, brochure.

[4] Cambridge Instrument Company, list No. 144.

[5] H. A. Daynes, *Gas Analysis by Measurement of Thermal Conductivity*, (Cambridge University Press, London, 1933).

[6] R. H. Munch, "The analysis of gases by thermal conductivity methods," Ind. and Eng. Chem., Ind. Ed. 37, 85 (Aug. 1945).

[7] E. Woods and H. Helmholtz, Mayo Clinic, Demonstration, Rochester, Minnesota, Sept. 1948.

[8] A. Hemingway, A. O. Nier and R. Varco, University of Minnesota, Demonstration, Minneapolis, Minnesota, Sept. 1948.

[9] R. W. Stacy, J. A. Hunter, and F. A. Hitchcock, "A Mass spectrometer for the rapid continuous analysis of respiratory gases," Am. Physiol. Soc., 57th Ann. Meeting, Atlantic City, New Jersey.

[10] J. C. Lilly, NRC-CAM Report No. 299; also: Army Air Forces, Air Materiel Command, Eng. Div., Memorandum report on nitrogen meter, August 30, 1946, Ser. No. TSEAA-660-107.

[11] J. C. Lilly, "Studies on the mixing of gases within the respiratory system with a new type nitrogen meter," Fed. Proc. 15, No. 1 (March 1946).

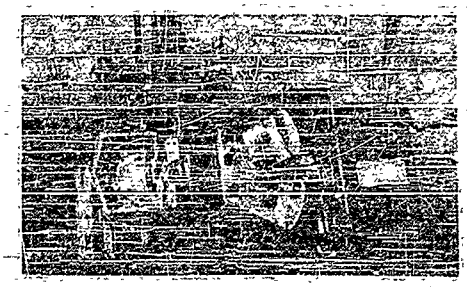

FIG. 3.

will have a time lag of the same order as the mass spectrograph and many of the same criticisms apply, but it is quite versatile and should be capable of considerable accuracy.

(f) The interferometric method,[12] while reportedly very accurate, requires constant manual adjustment and has a response lag of the order of 25 seconds.

(g) The paramagnetic oxygen analyzer[13, 14] has proven to be a highly satisfactory device and is available commercially in a very reliable form[15] but is limited in usefulness and has a time lag of the order of 15 seconds.

(h) The optical gas analyzers, principally infra-red,[16] depend on the unique absorption bands of the various gases, and consequently are limited in their usefulness to those having sufficiently strong absorption in a useful range. In addition, their time response is limited to the rate of response of available infra-red detectors. The instruments on the market at present require a considerable volume of sample[17, 18, 19] resulting in a poor volume-composition "resolution," and are relatively slow. An infra-red "acoustic" device has been described, but has not been developed commercially.[20] A new instrument, developed by Phillips Laboratories, seems to have eliminated most of the objectionable features, but is expected to be quite expensive and is not available commercially as yet. British devices utilize a similar method and are available.[21] A further exposition of the problem is adequately covered by Fastie and Pfund[22] and Williams.[23]

An infra-red gas analyzer has been developed in this laboratory which has been found useful for a number of gases of physiological importance, including carbon dioxide, ether, carbon monoxide, acetylene, and others, and no trouble has been encountered with interference including that from water vapor. The principle features which make this instrument useful are: (a) the use of crossed beams from a common source to keep the sample as small as possible and to reduce the effect of variations of source temperature, (b) the use of inert mica windows (wave-length-transmission curve, Fig. 1)

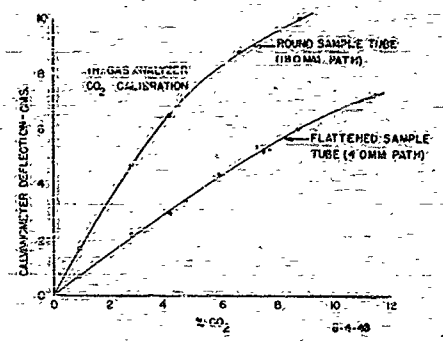

FIG. 4.

which allow the passage of near infra-red energy without hygroscopic or chemical action, and (c) the use of a rapid, sensitive detector made possible by Western Electric's "SETT" element, a "therm'stor" bolometer. The use of selective filters may prove useful but have not been found to be essential.

The apparatus is shown schematically in Fig. 2, and as built in Fig. 3. The source (S) is a helix of nichrome wire heated electrically (40 watts) and operated at a bright red heat, and the supports and box are water cooled to reduce temperature effects. The two spherical concave front surfaced aluminized or evaporated gold mirrors of 10-cm focal length (M_1, M_2), focus slightly enlarged superimposed images of the source at the center of the sample or breathing tube (T), which, for carbon dioxide, was constricted at this point to give a path length of about 4 mm in order to operate on the straighter first portion of the exponential concentration-absorption curve in the physiological range (0–9

[12] T. Benzinger and C. Kitzinger, "Photographische registrierung interferometrischer gas analysen," AAF Aero Med. Center, Heidelberg, Germany, 1946.

[13] L. Pauling, R. E. Wood, and J. H. Sturdivant, "An instrument for determining the partial pressure of oxygen in a gas," J. Am. Chem. Soc. 68, 795 (1946).

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[15] Arnold O. Beckman Company, Pasadena, California.

[16] E. D. McAlister, "Spectrographic method of measuring carbon dioxide concentration," Phys. Rev. 49, 704 (1936).

[17] Baird Associates, Cambridge, Massachusetts.

[18] Leeds and Northrup Company, Philadelphia, Pennsylvania.

[19] N. Nelson, The N.D.R.C. infra-red gas analyzer for the determination of rapidly changing CO concentrations, A.M.R.L. Proj. No. T-9, May 18, 1945.

[20] M. L. Vengerov, "An optical acoustic method of gas analysis," Nature (London), 158, 28 (1946); "Spectrophone," Comptes Rendus 46, 182–185 (1945).

[21] C. R. Barber, "Thermal and mechanical instruments shown at Physical Society's Exhibition," J. Sci. Inst. 24, 143 (1947).

[22] W. G. Fastie and A. H. Pfund, "Selective infra-red gas analyzers," J. Opt. Soc. Am. 37, 762 (1947).

[23] Van Z. Williams, "Infra-red instrumentation and techniques," Rev. Sci. Inst. 19, 135 (1948).

percent). The two beams then continue through the 5.0-cm gas filter cells (F_1, F_2) one of which contains a mixture of all interfering gases in the test sample and the other contains all but the gas to be measured. Since the path through the filter cell is so long, all interfering radiation is filtered out before reaching the detectors. The second pair of mirrors, also of 10-cm focal length, (M_1', M_2'), similar to the first but larger in diameter, reforms a considerably reduced image of the source on the sensitive area (0.2×2.0 mm) of the detectors (D_1, D_2). The size of the source and optical components are so chosen that this reduced image just a little more than covers the active area of the bolometers. The two adjustable opaque flags (B) following the filter cells are essential for balancing the radiant energy in the two beams or spurious deflections will result. The chamber containing the mirrors and bolometers was constructed so that an additional filter gas might be introduced here also.

Considerable attention was given to a suitable source, and while other means such as glass, oligoclase, etc.[24] might peak more energy at a particular absorption band, a considerable decrease in sensitivity would be experienced for another absorption band and furthermore, the high voltage and auxiliary heater made these cumbersome and dangerous. The Nernst glower proved quite fragile and short lived. Nichrome wire, operated at bright red heat, has a very broad peak at about 4 microns which extends relatively little into the visible and

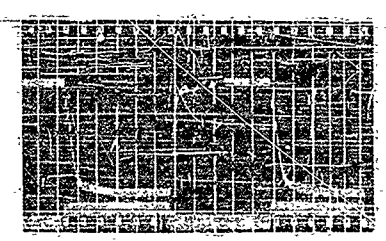

FIG. 5.

so is a good and convenient source.[25] No reason for replacement of the unit was noted after several hundred hours of severe operation.

The detectors were chosen for their sensitivity and their relatively high speed of response. Other detectors, considerably less expensive may be used at the sacrifice of speed. For a gas having an absorption band in the near infra-red, considerably cheaper and faster detectors may be used (lead sulfide, thaloïde cell).

The recorder consists simply of an electrocardiograph string galvanometer, sens. 1 mv per cm, 1500 ohm, with its associated camera, coupled to the high impedance bolometer bridge (each arm 3.0 megohms) through a single coupling vacuum tube with its steady state plate current bucked out. A more rugged pen recorder has been used in conjunction with a breaker type amplifier at the sacrifice of speed, but with greatly increased sensitivity. An indicating meter may thus be used for static measurements of isolated samples.

The calibration curve (Fig. 4) shows the effect obtained by decreasing the optical path through the breathing tube from 18 to 4 mm. The cylindrical tube first used, while quite simple, did not provide sufficiently linear response without extensive electrical compensation, and the short path (0.4 cm) flattened tube, proved quite satisfactory.

Figure 5 is included to indicate the electrical response (bolometer, circuit and galvanometer) obtained by blocking a very small portion of the radiation to one bolometer by means of a small signal magnet, thereby unbalancing the circuit to simulate blocked radiation. Simultaneously another signal magnet interrupted the beam to the camera. The two magnets were interchanged in order to rule out possibility of variations in response and similar results were obtained. The vertical time markers are 0.2 second apart. This shows a 90 percent electrical response in about 0.1 sec. and a slow rise for about 0.4 sec. The over-all response is very nearly the same. The irregularity on the descending portion of one record was due to chattering of the signal magnet.

A record of CO_2 of the respired air during a normal and complete expiration of a normal person is shown in Fig. 6 together with the expired velocity. The over-all speed of response is shown on inspiration where the CO_2 curve drops quickly to the base line. The inspiratory phase is designated by the flat portion of the velocity curve. The lag between the onset of expiration and rise of the CO_2 curve corresponds very closely to the volume of air trapped in the portions of the respiratory tree where gaseous exchange does not take place, the so called "dead space." The continued rise during expiration has

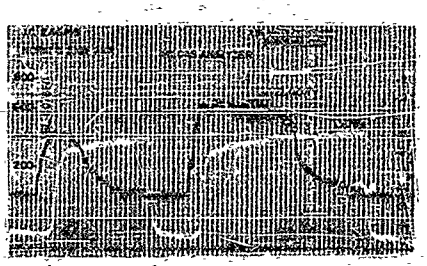

FIG. 6.

[24] W. W. Coblentz, Supplementary investigations of infra-red spectra, Carnegie Institution of Washington, 1908.
[25] General Electric Company, Lamp Bulletin.

been explained by the continuous diffusion of CO_2 into the lungs from the blood. Variations in this pattern have been found.

This device is believed to have a number of advantages over those existing. These are: (a) relatively low cost, (b) rapidity of response, (90 percent of maximum in 0.15 second over-all), (c) ease of recording, (d) full scale sensitivity obtained with fairly linear response from 0–9 percent CO_2, and (e) insensitiveness to normal pressure and temperature variations. The unit may be used with a number of gases mentioned and with proper alignment and construction, simultaneous measurements may be made of a number of gases.

The need and basic idea for such an analyzer was first brought to our attention by Professor W. O. Fenn, Department of Physiology. In addition to acknowledged sources of information, further material help and suggestions have been made by Dr. B. O'Brien, Colonel A. Gee, Dr. F. Paul, and Mr. W. Klinkert of the University of Rochester, Department of Optics; Dr. A. F. Turner and Staff of the Bausch and Lomb Optical Co.; and Dr. H. Rahn, Dr. A. B. Otis, Dr. H. A. Blair, Dr. W. S. McCann, and Mr. G. Rosenworth and numerous others at the University of Rochester Medical Center. The work was made possible by a fellowship from the John and Mary R. Markle Foundation and was supported in part by the Air Materiel Command at Wright Field.

A THEORETICAL STUDY OF THE COMPOSITION OF THE ALVEOLAR AIR AT ALTITUDE[1]

WALLACE O. FENN, HERMANN RAHN AND ARTHUR B. OTIS

In our studies of high altitude physiology we have found an oxygen-carbon dioxide diagram a very great aid to accurate thinking. It has been useful in so many different problems that we consider it worth while to describe it in this paper so that it can be made available to others.

1. *Breathing pure oxygen.* In this diagram the alveolar tensions of carbon dioxide are plotted as ordinates against the alveolar tensions of oxygen as abscissae as in figure 1, which represents the situation when an aviator ascends to high altitudes breathing pure oxygen. At any altitude, breathing pure oxygen,

$$pCO_2 + pO_2 = p'O_2 \qquad (1)$$

where $p'O_2$ refers to the tension of oxygen in the inspired air (BTPS or body temperature, saturated, ambient pressure) and the other tensions refer to alveolar air (BTPS). This equation gives a family of parallel diagonal lines on the chart each of which represents a given altitude such that $B - 47 = p'O_2$. The intercepts of these diagonals on the X axis represent therefore values of $B - 47$. With the aid of Henderson's nomogram for the blood of A.V.B. or any other similar data it is possible to assign a given percentage saturation of the arterial blood to every point on the chart. Thus lines of equal arterial saturation can be drawn. To indicate the location of such a family of curves the 65, 75, 85 and 95 per cent saturation lines have been drawn. When the saturation becomes less than about 65 per cent the subject is almost certain to lose consciousness very soon and this region of the chart has therefore been labelled "anoxia."

To show the normal behaviour of an aviator in going to progressively higher altitudes the line marked "alveolar air" has been drawn to indicate the successive positions of the alveolar air composition as the altitude is increased from ground level to above 43,000 feet. The curve bends downward after passing the 95 per cent saturation line because of the hyperventilation caused by the stimulus of anoxia. Hyperventilation at 43,000 feet moves the alveolar point

[1] This work was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Rochester.

down on the corresponding diagonal so that the pCO_2 is decreased about 10 mm. Hg and the pO_2 is increased a corresponding amount. If the pCO_2 is lowered too far by hyperventilation the symptoms of acapnia develop. A line marking this threshold has been drawn on the diagram at 20 mm. Hg although the level varies considerably with different individuals and different durations of exposure.

So long as the rate of CO_2 output remains constant alveolar pCO_2 will vary inversely with alveolar ventilation. On this assumption a scale of ventilation

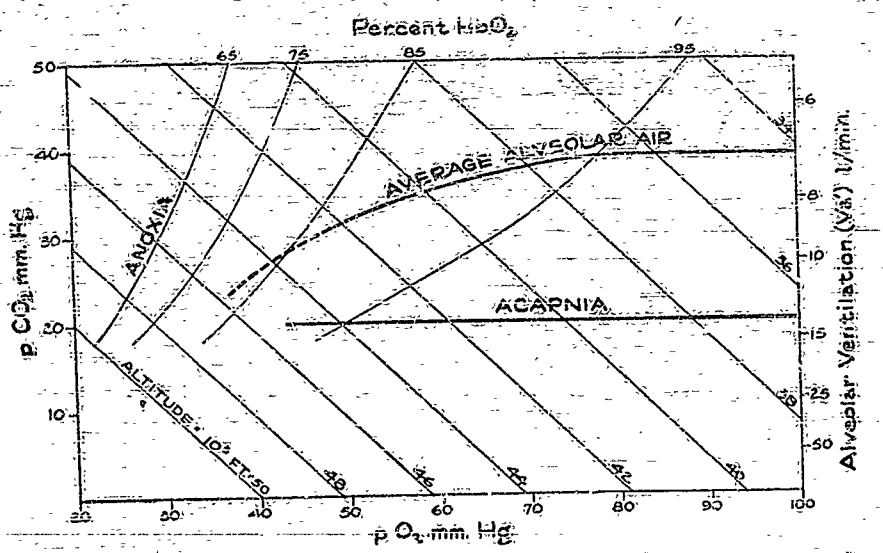

Fig. 1. Alveolar pCO_2 as ordinates plotted against alveolar pO_2 as abscissae at different altitudes breathing pure oxygen. The average alveolar air line was taken from analyses of alveolar air samples forcibly exhaled beginning at the end of a normal expiration. The pCO_2 values were 39 mm. at 30,000 ft.; 34.8 mm. at 40,000 ft.; and 32 mm. at 42,000 feet. The figures are averages of 16, 19, and 21 determinations respectively. The scale of alveolar ventilation at the right is calculated by equation 17 on the basis of a rate of CO_2 output of 315 cc. per minute (S.T.P.).

rates has been indicated at the right of the diagram. The values were calculated according to the equation

$$V_a' = \frac{272}{pCO_2} \qquad (2)$$

where 272 is a constant (see equation 17 and discussion), V_a' is the alveolar ventilation (BTPS) in liters per minute and

$$V_a' = \text{total ventilation } (V_t) - (\text{dead space} \times \text{frequency})$$

Actually of course the CO_2 output does not remain constant at altitudes where hyperventilation occurs because extra CO_2 is blown off. Temporarily this will invalidate the equation given above until the R.Q. returns to normal. A rigid derivation of a ventilation equation to take account of this situation will be given below.

The chart in figure 1 represents the simplest condition. When air instead of oxygen is breathed the diagram is much more complicated but it is for the understanding of these same complications that the diagram is particularly useful.

2. *The alveolar air equation.* To understand the air-breathing diagram it is necessary to develop the alveolar air equation.

Let V = a volume of moist inspired air in milliliters

y = milliliters of moist CO_2 added to V in the lungs

x = milliliters of moist O_2 removed from V in the lungs

$C = CO_2$ and $O = O_2$

f = the fraction of moist gas in alveolar air (by volumes)

pC and pO = partial pressures of C or O in alveolar air in mm. Hg

f' and p' refer to moist inspired air

Q = respiratory quotient as observed $= \frac{y}{x}$

$V + y - x$ = the new volume after transition from tracheal to alveolar air.

$$y = fC(V + y - x) - f'CV$$
$$x = f'OV - fO(V + y - x)$$

Substituting Qx for y and $\frac{y}{Q}$ for x

$$x = \frac{f'OV - fOV}{1 + fOQ - fO} \tag{3}$$

$$y = \frac{fCV - f'CV}{1 - fC + \frac{fC}{Q}} \tag{4}$$

Substituting these values of x and y in the equation $\frac{y}{x} = Q$ and solving for fO gives

$$fO = \frac{f'OQ + fCf'O(1 - Q) + f'C - fC}{f'C(1 - Q) + Q} \tag{5}$$

Multiplying both sides by $(B - 47)$ to change f to p we have

$$pO = \frac{p'OQ + pCf'O(1 - Q) + p'C - pC}{f'C(1 - Q) + Q} \tag{6}$$

This is the complete alveolar air equation but if CO_2-free gas is inhaled and $f'C = 0$ it can be simplified to[2]

$$pO = p'O + \frac{pCf'O(1 - Q)}{Q} - \frac{pC}{Q} \tag{7}$$

If pure oxygen instead of air is inhaled and $f'O = 1$; or if $Q = 1$, whatever the value of $f'O$ then

$$pO = p'O - pC \tag{8}$$

[2] This same equation has been given by Boothby in the Handbook of Respiratory Data, (Washington, D. C., 1944) where prior credit is given to several other authors. (See Essay A.)

Since equation 8 is identical with equation 1 used for the altitude diagonals in figure 1 it is evident (1) that this chart is applicable to oxygen-breathing altitudes regardless of the RQ and (2) that if the R.Q. = 1.0 the chart is also applicable to the problems involved in the breathing of air.

3. *Breathing air.* Equation 7 represents the condition where CO_2-free air is inhaled which is practically true of ordinary air. The application of this equation to the oxygen-carbon dioxide diagram is illustrated in figure 2. The altitude of 10,000 feet is now represented by a family of diagonals all radiating from a pO'_2 value of 100 mm. Hg, this being the oxygen tension in the moist inspired air. There is a different diagonal for each R.Q. value and at each altitude there

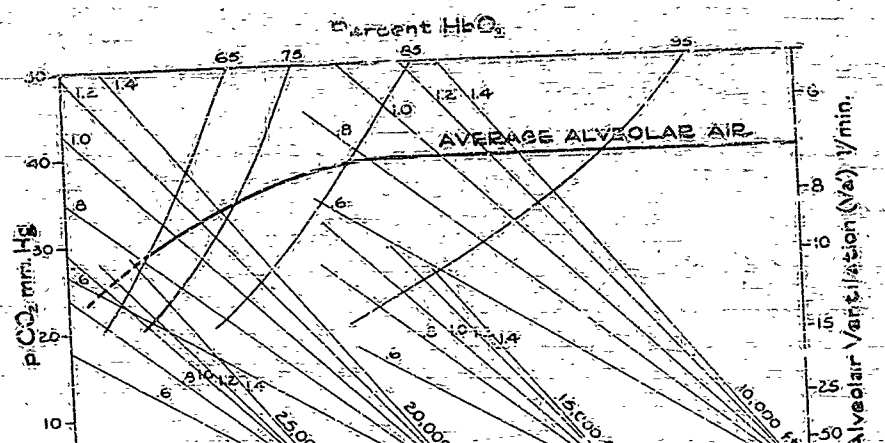

Fig. 2. Alveolar pCO_2 and pO_2 at different altitudes breathing air. Families of diagonals for 4 different altitudes are shown. Each line represents a certain R.Q. value as indicated on the graph and was calculated from equation 7. The scale of alveolar ventilation at the right is calculated by equation 17 on the arbitrary assumption that the rate of CO_2 output is 315 cc. per minute (S.T.P.). The average alveolar air line is based upon analyses of large numbers of samples exhaled forcibly beginning at the end of a normal expiration. Data will be published elsewhere.

is a similar set of diagonals. Four such sets of Q diagonals have been drawn in figure 2 for four different altitudes. The position of the alveolar air on any one of these diagonals will depend upon the rate of breathing and the rate of CO_2 output. The scale on the right indicates the alveolar ventilation for each pCO_2 level on the assumption that the CO_2 output is constant at 315 cc. per minute. This value was arbitrarily selected. For other values the ordinates are changed in proportion.

It is obvious that the diagonals of one altitude intersect some of the diagonals of a slightly higher or lower altitude. At one of these points of intersection therefore the subject might be at 20,000 feet with an R.Q. of about 1.4 due to

overventilation and a lowered pCO_2 or he might be at 15,000 feet with an R.Q. of about 0.8. This illustrates the difficulty of calculating what altitude is equivalent to a given low-oxygen nitrogen mixture. Strictly speaking it is impossible to calculate such equivalent altitudes without specifying the rate of breathing and the R.Q. (See also fig. 5.)

A full set of altitude diagonals for 20,000 feet breathing air is shown in figure 3. If equation 7 is solved for Q

$$Q = \frac{pC(1 - f'O)}{p'O - pO - f'OpC} \tag{9}$$

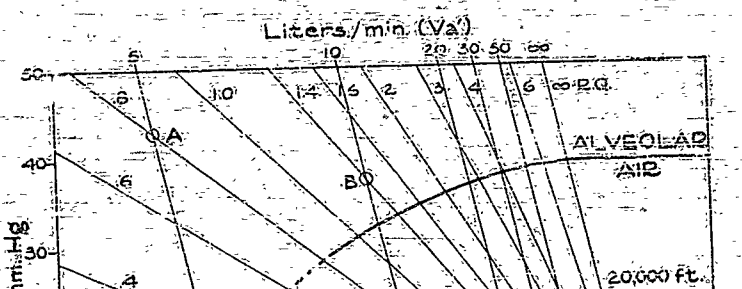

Fig. 3. Alveolar air diagram for 20,000 feet breathing air. Each diagonal line starting at $pO_2 = 65$ represents a given R.Q. as indicated on the diagram and was calculated from equation 7. The nearly vertical parallel lines represent points of equal alveolar ventilation calculated by equation 15 on the arbitrary assumption that the rate of oxygen consumption, $\dot{X}_o$, equals 315 cc per min. The average alveolar air line is the same as that in figure 2. The R.Q. $= \infty$ and $\dot{V}_A = \infty$ lines are identical and have a reciprocal slope of $0.2093 = f'O$. For points *A*, *B* and *C* see text p. 646.

Obviously $Q = \infty$ when the denominator $= 0$ or when $p'O - pO = f'OpC$. The negative (reciprocal) slope of the $Q = \infty$ diagonal is therefore $f'O$. The iso-ventilation lines which are also included in figure 3 will be discussed later.

It is instructive to inquire what happens to the R.Q. diagonals when the percentage of oxygen in the inspired air increases. For the sake of simplicity it may be assumed that the barometric pressure is so adjusted that at all percentages the tension of oxygen in the inspired air (X intercept) remains constant. This assumption however is immaterial to the argument because slopes of the R.Q. diagonals are identical at all values of $p'O$ for the same value of $f'O$.

From figure 4 it can be seen that when $f'O_2$ (i.e., the fraction of O_2 in the inspired air) increases, the R.Q. diagonals come closer together until when $f'O_2 = 1.0$ they all coincide with the R.Q. = 1.0 diagonal. Thus when pure O_2 is breathed the alveolar air must lie along a single diagonal regardless of the R.Q. On the graphs in figure 4 two special alveolar points are indicated by circles: (1) at $pCO_2 = 40$ and $Q = 0.8$ and (2) at $pCO_2 = 25$ and $Q = 1.5$. Point 1 is a normal and point 2 is one that could easily be reached temporarily by overventilation without danger of serious hypocapnia. It is significant that the gain in pO_2 in this process is 33 mm. Hg at 6 per cent, 31 mm. at 21 per cent, 24 mm. at 60

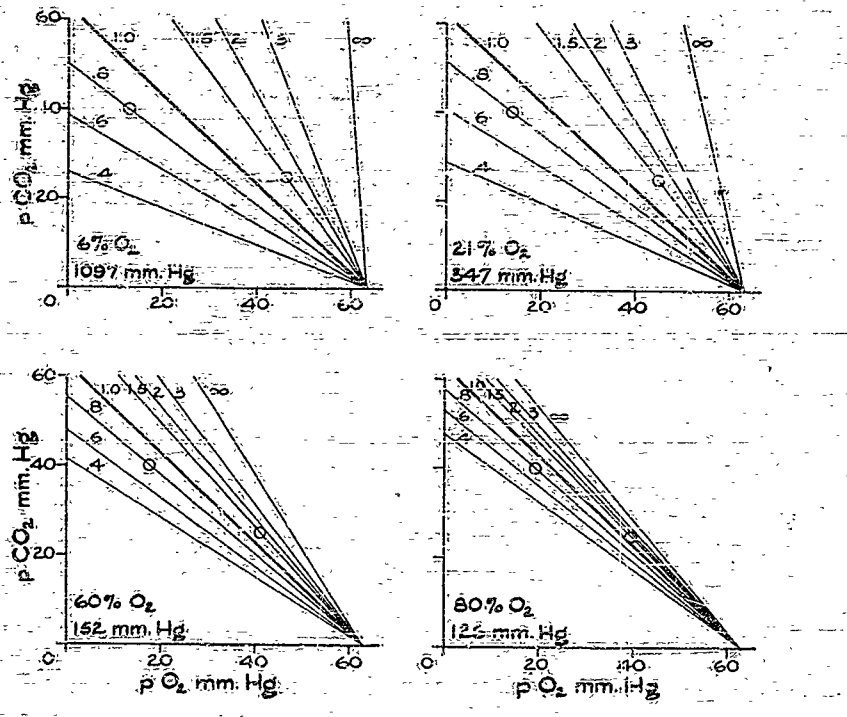

Fig. 4. R.Q. diagonals at different altitudes (pressures) and breathing gas mixtures of different oxygen percentages so that the inspired $pO_2 = 63$ mm. Hg in each case. Each line is calculated according to equation 7. The spread diminishes as the oxygen percentage increases. See text for discussion of points marked by circles.

per cent, 20 mm. at 80 per cent O_2 and only 15 mm. at 100 per cent O_2. At air-breathing altitudes therefore the immediate benefit (in terms of pO_2 gain) derived from overventilation may be twice as great in terms of alveolar oxygen tension as at oxygen-breathing altitudes and this difference depends upon the spreading of the R.Q. diagonals.

4. *Equivalent altitudes.* The difficulty involved in calculating what mixture of O_2 and N_2 is equivalent to a given altitude is illustrated by figure 5. The solid lines represent R.Q. diagonals at 20,000 feet breathing air. The same inspired $p'O_2$ can be obtained by an 8.83 per cent O_2 + 91.17 per cent N_2 mixture

at sea level but the R.Q. diagonals on such a mixture differ appreciably as indicated by the dotted lines. At equal rates of ventilation therefore the alveolar air would not be the same under the two conditions unless the R.Q. = 1.0. Furthermore at the same R.Q. (except when $Q = 1$) it would be impossible to breathe in such a way that the alveolar composition would be the same at ground level on low O_2 as at altitude on air. This is obvious because the R.Q. diagonals for the two conditions do not cross except at infinite ventilation rates (i.e., at $pC = O$). This illustrates convincingly the possible fallacies involved in the common expedient of simulating high altitude conditions by low oxygen mixtures.

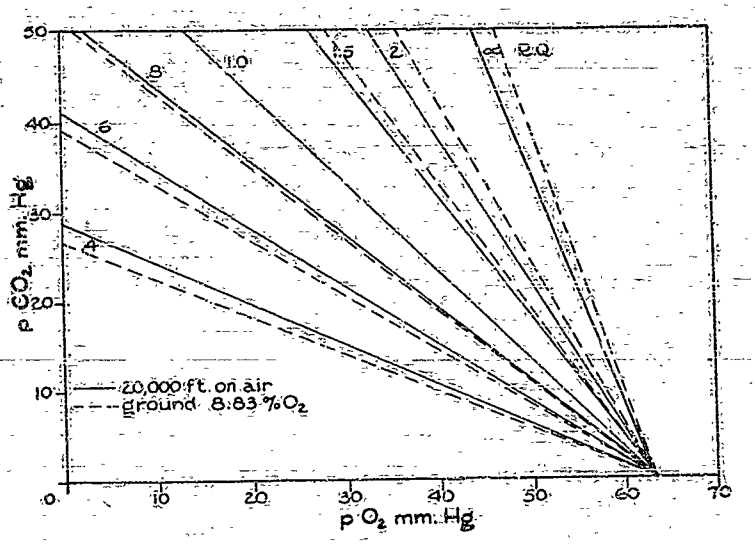

Fig. 5. Difference between 20,000 feet breathing air (solid lines) and an 8.85 per cent oxygen mixture in nitrogen at ground level having the same inspired pO_2. The dotted and solid R.Q. diagonals diverge more and more as the R.Q. becomes greater or less than 1.0. This illustrates the problem of calculating equivalent altitudes. See text. Each line is calculated according to equation 7.

Similar difficulties are encountered if the condition of breathing air at 20,000 feet is simulated by inhaling pure O_2 at 100 mm. Hg where the inspired pO_2 is again the same. In this case the alveolar air must lie along the $Q = 1$ diagonal regardless of the actual value of Q, and the discrepancies between the two conditions are therefore still larger than in the previous comparison. In order to simulate 20,000 feet breathing air by pure O_2 at a higher altitude it is necessary to select an altitude for pure O_2 such that the $B - \frac{47}{}$ value is equal to $pC + pO$ for the alveolar air at 20,000 feet. If then the R.Q. and CO_2 output can be assumed to remain the same at both altitudes, the alveolar air will be the same provided the ventilation is so regulated that the alveolar pCO_2 is also the same.

5. *The ventilation equation.* The intercept of one of these R.Q. diagonals on the x axis represents the oxygen tension of the moist inspired air. When the air enters the alveoli the oxygen tension diminishes and the carbon dioxide ten-

sion increases and the point on the chart which represents the composition of the alveolar air moves up to the left along one of these diagonals. If the rate of breathing is very fast it will not move very far up the diagonals because the air will not remain long in contact with the alveolar walls. If the rate of breathing is "normal" the pCO_2 will be "normal" and the alveolar air composition will lie along the average alveolar air line shown in the chart (fig. 2 or 3). If the rate of breathing is infinitely fast the alveolar air will have the same composition as the inspired air. It should be possible, therefore, to draw a series of lines across the chart which represent equal rates of ventilation. The derivation of equations for plotting these lines must now be considered. At air breathing altitudes this is somewhat more complicated than it is for pure oxygen. The problem is much simplified in the beginning if only alveolar ventilations are concerned. The total ventilation can always be obtained by adding the dead space ventilation which is equal to the product of dead space volume and the frequency of breathing. Let Y and X = rates of CO_2 output and O_2 intake respectively in cubic centimeters per minute at BTPS.

$\dot{X}_0$ = O_2 intake in cc. per minute at 0°C. dry, 760 mm. Hg

Y_0 = CO_2 output in cc. per minute, at 0°C. dry, 760 mm. Hg

V_a = Alveolar ventilation in cc/min at BTPS, V_t = total and V_d = dead space ventilation. $V_t = V_a + V_d$.

V_a' = alveolar ventilation in liters per min. at BTPS.

$$\text{Now } Y = V_a fC \tag{10}$$

and

$$fC = \frac{y}{V + y - \frac{\dot{x}}{Q}} = \frac{y}{V + y - \frac{\dot{y}}{\dot{Q}}} \tag{11}$$

Substituting (11) in (10)

$$Y = \frac{V_a y}{V + y - \frac{\dot{y}}{\dot{Q}}} \quad \text{or } y = \frac{QVY}{QV_a - QY + Y}$$

Putting this value of y equal to that in equation 4 and solving for V_a

$$V_a = \frac{Y(Q + f'C(1 - Q))}{Q(fC - f'C)} = \frac{\dot{X}(Q + f'C(1 - Q))}{fC - f'C} \tag{12}$$

Now

$$\dot{X}_0 = X\frac{273}{310} \times \frac{B - 47}{760}$$

$$V_a = 1000\, V_a'$$

$$fC = \frac{pC}{B - 47} \quad \text{and } f'C = \frac{p'C}{B - 47}$$

Substituting these values for X, V_a, and (in the denominator) fC and $f'C$ in equation 12 we have

$$V'_a = \frac{0.864X_0(Q + f'C(1 - Q))}{pC - p'C} \tag{13}$$

The equation is more useful when expressed in terms of X_0 because this may reasonably be assumed to remain constant while Y_0 varies with the rate of breathing. While this equation expresses the ventilation in terms of CO_2 tension it can also be expressed in terms of O_2 tension by the same method. Thus in equation (14)

$$fC = \frac{y}{V + y - x} = \frac{Qx}{V + Qx - x} \tag{14}$$

This value of fC is substituted in (10) and solved for x. The resulting equation is combined with (3) and solved for V_a to obtain

$$V'_a = \frac{0.864\ X_0(1 - f'O(1 - Q))}{p'O - pO} \tag{15}$$

If $f'O = 1$, then $f'C = 0$ and from (15)

$$V'_a = \frac{0.864\ X_0 Q}{p'O - pO} \tag{16}$$

If $f'C = 0$ then from (13)

$$V'_a = \frac{0.864\ X_0 Q}{pC} = \frac{0.864\ Y_0}{pC} \tag{17}$$

If $Y_0 = 315$ cc. CO_2 per minute equation 17 is identical with equation 2. Thus, when the CO_2 output is assumed constant and $p'C = 0$, the lines of constant ventilation of the pCO_2-pO_2 chart are parallel to the X axis for all altitudes, according to the scale shown in figure 1.

6. *Oxygen isoventilation lines (when X_0 is constant).* Equations 12 and 15 express the alveolar ventilation in terms of the R.Q. On a chart like that in figure 2 they would permit the calculation of the alveolar ventilation which would be necessary to reach a given pCO_2 value (equation 13) or a given pO_2 value (equation 15) on a specified R.Q. diagonal at any altitude. In order to draw an isoventilation *line* on such a chart it is necessary to combine these two equations with the elimination of Q. This results in the following

$$V'_a = \frac{0.864\ X_0(1 - f'O - f'C)}{(1 - f'C)(p'O - pO) - f'O(pC - p'C)} \tag{18}$$

Or, rearranging,

$$pO = p'O + \frac{f'Op'C}{1 - f'C} - \frac{0.864\ X_0(1 - f'O - f'C)}{V'_a(1 - f'C)} - \frac{f'OpC}{1 - f'C} \tag{19}$$

In equation 19 all the terms refer to the composition of the inspired air at a given altitude except pO, pC, X_o and $\dot{V}a'$. The equation gives therefore the composition of the alveolar air which would be expected from a given set of conditions if the rate of oxygen consumption and the alveolar ventilation are known. If pO and pC are the only variables then this is the equation of a straight line of reciprocal slope equal to $-\frac{f'O}{1-f'O}$ (in the last term) and the intercept on the X axis is given by the first 3 terms on the right side of the equation.

When CO_2 is absent from the inspired air, equation 19 may be simplified to

$$pO = p'O - \frac{0.364\,X_o(1-f'O)}{\dot{V}a'} = f'O\,pC \qquad (20)$$

When in addition, $f'O = 1$ the equation becomes $pO = p'O - pC$. This means that in pure O_2 the alveolar air is always somewhere on this diagonal regardless of the values of $\dot{V}a'$, $\dot{V}_{O_2}$, or Q.

A set of isoventilation lines plotted from equation 20 for a subject breathing air at 20,000 feet is shown in figure 3. All the lines are parallel and have a negative slope of 0.209 which is the fraction of oxygen in the inspired air ($f'O$). The line for $\dot{V}a' = \infty$ is seen to coincide with the line for $Q = \infty$.

The beneficial effect of high R.Q. due to overventilation at altitude is well illustrated by figure 3. Point A indicates that a subject at this altitude with a rate of oxygen consumption of 315 cc. per min. and an R.Q. of 0.8 who is breathing so as to provide 5 liters per minute of alveolar ventilation will have an alveolar pCO_2 of 42 mm. (This is slightly higher than normal but will illustrate the principle.) If now the alveolar ventilation is increased to 10 liters per minute the alveolar CO_2 tension will decrease and the R.Q. will increase possibly to 1.4 so that the alveolar air will be represented by point B, the pO_2 being 22 mm. greater than at A. If the same ventilation rate is maintained for a half hour or more the R.Q. will gradually fall as excess CO_2 is blown off until it returns to the normal value of 0.8 as represented by point C.

It is important to note that this temporary gain in pO_2 due to hyperventilation is largely dependent upon the presence of nitrogen in the air. If pure O_2 had been inhaled the point B would have been on the same diagonal as points A and C (i.e., the $Q = 1$ diagonal) each point being at the same pCO_2 level as in figure 3; and the gain in pO_2 would have been correspondingly less as shown in figure 4. The greater the oxygen percentage, the more nearly the R.Q. diagonals and the O_2 isoventilation lines coincide with the $Q = 1$ line and the less the temporary gain in pO_2 with hyperventilation.

Another way to explain this R.Q. effect is as follows. When pure O_2 is inhaled the CO_2 which escapes into the lung must displace O_2 in equal amounts so that a 10 mm. increase in pCO_2 leads to a 10 mm. decrease in pO_2. When air is inhaled however an increase of 10 mm. pCO_2 in the lungs leads approximately to a decrease of pN_2 of 7.9 mm. and a decrease of pO_2 of only 2.1 mm. The slope of the O_2 isoventilation lines in figure 3 indicates a loss of 2.1 mm. of pO_2 for a gain of 10 mm. of pCO_2. Thus when overventilating with inspired

air the resulting high R.Q. and increased CO_2 output has the advantage that it maintains the pCO_2 at a comfortable level without appreciably diminishing the gain in pO_2.

Or conversely, it may be said that in air, the same gain in pO_2 is obtained with less increase in ventilation than in pure O_2. After the high R.Q. due to anoxic hyperventilation has returned to normal (point C, fig. 3) there is little difference between pure O_2 and air in this respect. For a fall of 10 mm. in the pCO_2 there is a (permanent) gain of 10 mm. in pO_2 when pure oxygen is inhaled and a gain of about 12 mm. pO_2 in air if the R.Q. is 0.8. It is well known that this initial R.Q. effect is a very important factor in the maintenance of consciousness for short periods at extreme altitudes in air. The principle is not new but is here demonstrated in a novel way.

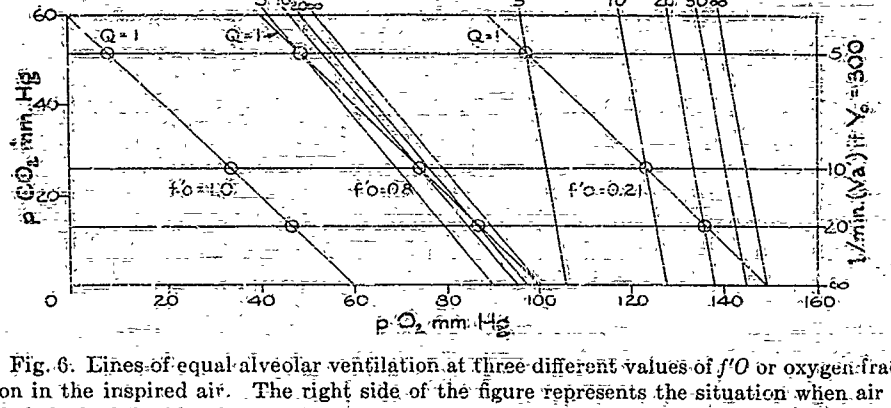

Fig. 6. Lines of equal alveolar ventilation at three different values of $f'O$ or oxygen fraction in the inspired air. The right side of the figure represents the situation when air is inhaled, the left side, the case for pure oxygen, and the family of lines in the middle represents 80 per cent oxygen. (See text.)

It has been shown in figure 4 that the R.Q. diagonals approach the $Q = 1$ line when $f'O$ approaches 1.0. The same is true of the oxygen ventilation lines calculated from equation 15 or 19 when X_o is constant. This result is illustrated graphically in figure 6 where 3 sets of diagonals are plotted for $f'O = 0.21$, 0.8 and 1.0. These are plotted arbitrarily at different $p'O_2$ values but this makes no difference because the slopes of the lines are not influenced by the absolute pO_2 but only by the O_2 percentage, $f'O$ as shown by equation 20. In this graph the points of intersection of the iso-ventilation lines and the diagonal $Q = 1.0$ are marked by circles. For the same ventilation rate these intersections are all at the same pCO_2 value at all altitudes. Thus as $f'O$ approaches 1.0 these iso-ventilation lines rotate anticlockwise about these marked intersections until at $f'O = 1.0$ in pure oxygen they coincide with the $Q = 1.0$ diagonal.

7. *Carbon dioxide isoventilation lines* (i.e., when Y_o is constant). The iso-ventilation lines shown in figure 3 were derived on the assumption that the rate of oxygen consumption is constant. Passing along one of these lines from low

to high CO_2 tensions it is found that the pO gradually diminishes as the R.Q. increases. The reason for this is that at the higher R.Q. values the rate of CO_2 output is greater for the same amount of O_2 taken out. As more CO_2 comes into the lungs from the blood per minute the volume of air that comes into the lungs from the trachea is correspondingly diminished because there is less decrease in volume due to oxygen absorption. Hence the oxygen in the alveoli is not renewed so rapidly and the oxygen tension falls.

When the rate of carbon dioxide output is assumed to be constant a very different set of isoventilation lines results. This can be shown by replacing

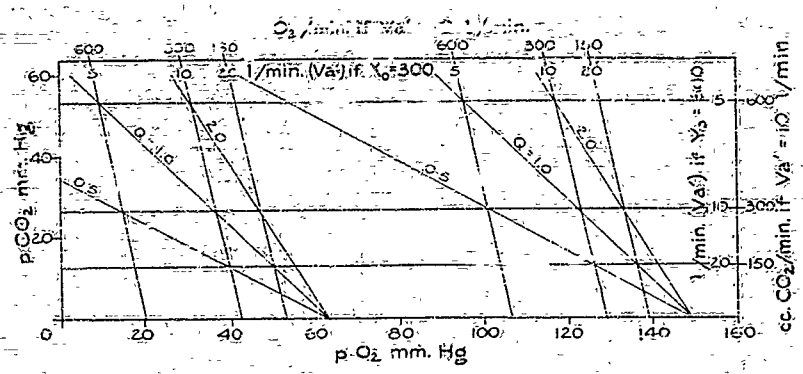

Fig. 7. Alveolar air chart for 20,000 feet (left) and ground level (right) breathing air showing R.Q. diagonals 0.5, 1.0 and 2.0 for each altitude. The chart shows the relationship between isoventilation lines (nearly vertical) when the O_2 intake is assumed constant and those (horizontal) when the CO_2 output is constant.

X_0 by Y_0/Q in equations 13 and 15, and then combining them as before with the elimination of Q. This results in the following

$$V'_a = \frac{0.864\, Y_0(1 - f'C - f'Q)}{(pC - p'C)(1 - f'Q) - f'C(p'O - pO)} \tag{21}$$

or, rearranging

$$pO = p'O + \frac{p'C(1 - f'O)}{f'C} + \frac{0.864\, Y_0(1 - f'C - f'O)}{V'_a f'C} - \frac{1 - f'O pC}{f'C} \tag{22}$$

Evidently these equations are very similar in form to equations 18 and 19. When $f'O = 1$ or when $f'C = p'C = 0$ equation 21 reduces to equations 16 or 17.

The two sets of isoventilation lines given by equations 18 and 21 may be called for convenience the oxygen and the carbon dioxide isoventilation lines respectively. The relation between them can be shown most simply when there is no CO_2 in the inspired air as illustrated in figure 7. In this graph R.Q. diagonals for $Q = 0.5$, 1.0 and 2.0 are drawn for two different altitudes breathing air. The oxygen isoventilation lines are drawn from equation 20 assuming that $X = 300$ cc. per min. and the carbon dioxide isoventilation lines, parallel to the X axis, are drawn from equation 17 assuming that $Y = 300$ cc. per minute.

When $Q = 1.0$ both Y_o and $X_o = 300$ and both the O_2 and CO_2 5 lit/min ventilation lines intersect at both altitudes on the $Q = 1.0$ lines. The same is true for the 10 and 20 lit/min lines. When however $Q = 2.0$ the 10 lit/min O_2 line intersects the 5 lit/min CO_2 ventilation line. But this is a 5 lit/min line only when $Y_o = 300$. Since $Q = 2.0$, Y_o in this case = 600 so the ventilation is really 10 lit/min at this point if $X_o = 300$ as indicated by the O_2 line. Con-

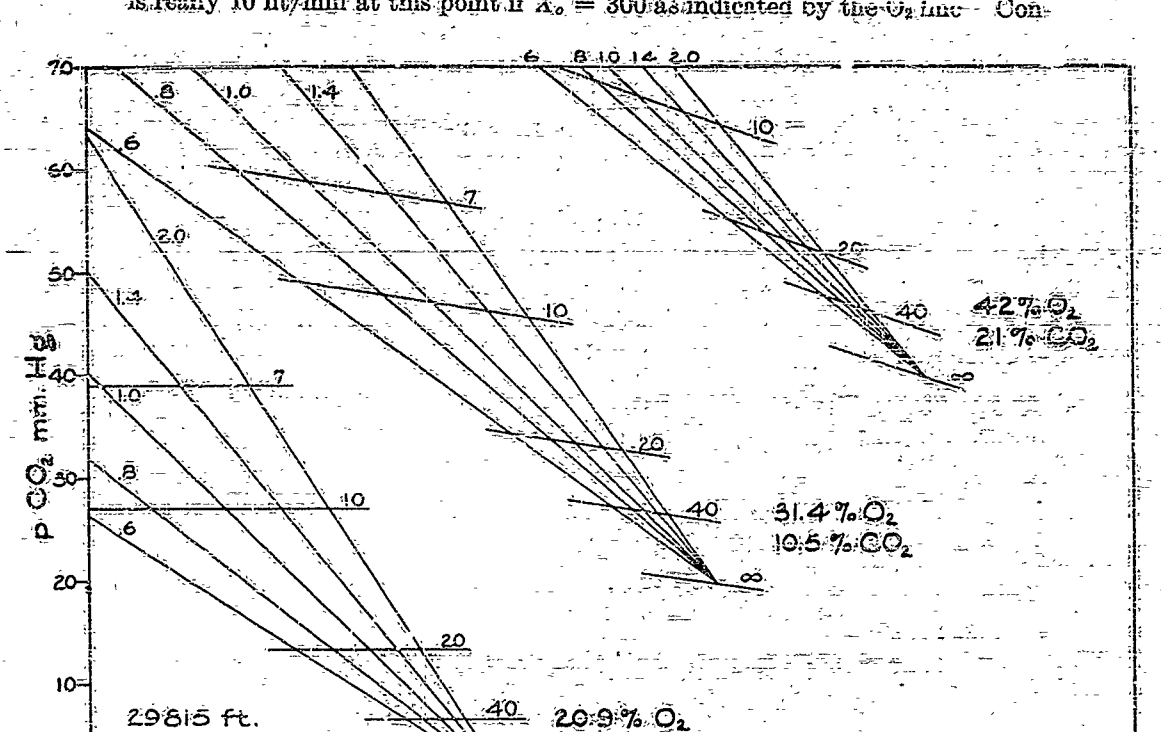

Fig. 8. The effect of adding CO_2 and O_2 to the inspired air. Three sets of R.Q. diagonals are shown for three different mixtures. All are calculated according to equation 6 for an altitude of 29,815 feet. The isoventilation lines traversing the R.Q. diagonals are calculated according to equation 22 assuming that the CO_2 output, $Yo = 315$ cc per minute. As the pCO_2 increases in the inspired air these lines deviate from the horizontal. Figures on these lines indicate the alveolar ventilation in liters per minute.

versely these ventilation lines may be regarded as lines of equal Y_o or X_o if the alveolar ventilation = 10 lit/min. The numerical values appropriate to this interpretation have been inserted in the figure. Thus the two 600 cc/min lines intersect on the diagonal $Q = 1.0$ but the 300 cc. X_o and the 600 cc. Y_o lines intersect on the $Q = 2.0$ diagonal.

8. *Ventilation when inspired air contains CO_2.* When the inspired air con-

trins a certain amount of CO_2 the carbon dioxide ventilation lines plotted from equation 22 are not parallel to the X axis but they have a reciprocal slope equal to $= \frac{1-f'O_2}{f'C}$. This is illustrated in figure 8 where three sets of R.Q. diagonals are represented for different mixtures of O_2 and CO_2 at 29,815 feet. The effect of adding 20 mm. of CO_2 to the inspired air is to raise the origin of the R.Q. diagonals by 20 mm. Breathing CO_2-free air in the lower left the CO_2 isoventilation lines are parallel to the X axis as in figures 6 and 7 and are drawn from equation 17 assuming that $\dot{V} = 315$ cc/min. In a 10.5 per cent CO_2, 31.4 per cent O_2 mixture the isoventilation lines have a slight slope to them and

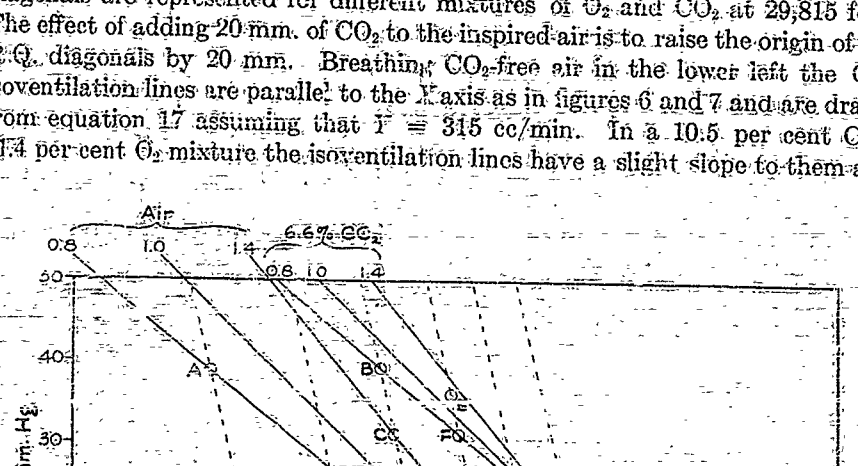

Fig. 9. Alveolar air chart illustrating the advantages of adding CO_2 to the inspired air at an altitude of 20,000 feet. Two sets of R.Q. diagonals are represented breathing air and air plus 6.6 per cent CO_2. Dotted lines represent isoventilation lines calculated by equation 19 on the assumption that the rate of oxygen intake, X_{O_2}, is constant at 315 cc/min. See text for the significance of the marked points.

this is more marked when the oxygen and the CO_2 are both still further increased. It may also be observed that as the nitrogen percentage decreases, the R.Q. diagonals come closer together as they did in figure 4 for oxygen alone. When the nitrogen percentage = 0 the CO_2 isoventilation lines coincide with the $Q = 1$ diagonal just as the O_2 isoventilation lines do. This can be seen from equation 22. When $f'O = 1$, then $f'C = 0$ and this equation reduces to $p\bar{O} = p'O = pC$ which is the equation for the $Q = 1$ diagonal.

9. *Advantages of inspired CO_2 at altitude.* It has been shown that a high R.Q. is advantageous at altitude because it permits a high ventilation rate and consequently a high alveolar pO_2 without serious hypocapnia. The same is true of CO_2 added to the inspired air. The benefit in other words is the same whether the CO_2 is exogenous or endogenous.

The advantage gained from adding CO_2 to the inspired air is shown in figure 9. Two sets of altitude diagonals are drawn for 20,000 feet. The lower set applies to the case where CO_2-free air is breathed. If now CO_2 is added to air at this altitude until the CO_2 tension is 20 mm., the CO_2 percentage will be 6.62 per cent and the oxygen will have been diluted to 19.5 per cent. The total dry pressure (B − 47) = 302 mm. The broken lines in figure 9 are O_2 isoventilation lines drawn from equation 19. With this particular CO_2 mixture made by diluting air the equation for the ventilation is the same whatever the amount of CO_2 added but this is a special case selected both because of its simplicity and because it is the most practical way of producing such a mixture for experimental purposes. If a subject goes to 20,000 feet without changing his rate of CO_2 output or his ventilation he would have an alveolar air composition represented by point A (assuming an R.Q. of 0.8). Due to the stimulus of anoxia he would increase his ventilation rate from 5.6 to perhaps 11.6 liters per minute and would move approximately to point C where his R.Q. is 1.4. If however he were to use a 6.6 per cent CO_2 mixture he would be at point B for the same rate of ventilation or at about point E if his ventilation were increased to 20 liters per minute. Both points C and E are only temporary because if the ventilation were to continue at the same rate the R.Q. would eventually return to 0.8 and the alveolar air would move to points D and F respectively. Point D would have the higher arterial saturation but it has the disadvantage of a considerable amount of hypocapnia. The performance would certainly be better at F than at D and probably better at E than at C. Point B is better than C because it can be maintained indefinitely but the arterial saturation is only about 67 per cent while at D it is about 90 per cent (see fig. 2 for saturation lines). At F however the saturation is 85 per cent and the pCO_2 is high enough for normal performance. Comparing points A and B it is evident that the addition of 20 mm. of CO_2 has increased the oxygen tension 20 mm. without decrease in the pCO_2. Comparing points B and D it is evident that at the same rate of ventilation the addition of 20 mm. of CO_2 to the inspired air has raised the alveolar pCO_2 21 mm. with a loss however of 5 mm. of pO_2.

The $Q = 1$ diagonal for 6.6 per cent CO_2 has been continued as a broken line to the X axis which it intersects at 79 mm. This represents the oxygen tension of the inspired air at an altitude of 15,137 feet. It may be said therefore as an approximation that the addition of this amount of CO_2 has lowered the equivalent altitude 4 or 5 thousand feet.

10. *Survival limits on the CO_2-O_2 diagram.* Finally it seems worth while to call attention to figure 10 which represents a CO_2-O_2 diagram on a much larger scale to include the lethal limits in all directions. The shaded area up to about 1 atmosphere of pO_2, represents the normal or physiological area. It is bounded on the top by the CO_2 narcosis level at about 50 mm. on the bottom by the acapnia threshold at about 20 mm. pCO_2 and on the left by anoxia at altitudes > 40,000 feet or tensions of O_2 < 100 mm. The corners of this shaded area are rounded off indicating that the effects of anoxia are additive to both high CO_2 and low CO_2. At an air pressure above 5 atmospheres the disorienting effects of high nitrogen concentration become noticeable (Behnke et al., 1935) and at

10 atmospheres or diving depths under water of 200 feet this nitrogen narcosis becomes severe. At 3 atmospheres of O_2 pressure oxygen poisoning becomes evident in some 2 hours of exposure and this effect is more severe at the higher CO_2 tensions. Thus high CO_2 is additive in its effects to both high O_2 and high nitrogen. The combination of high CO_2 with still higher O_2 pressures may

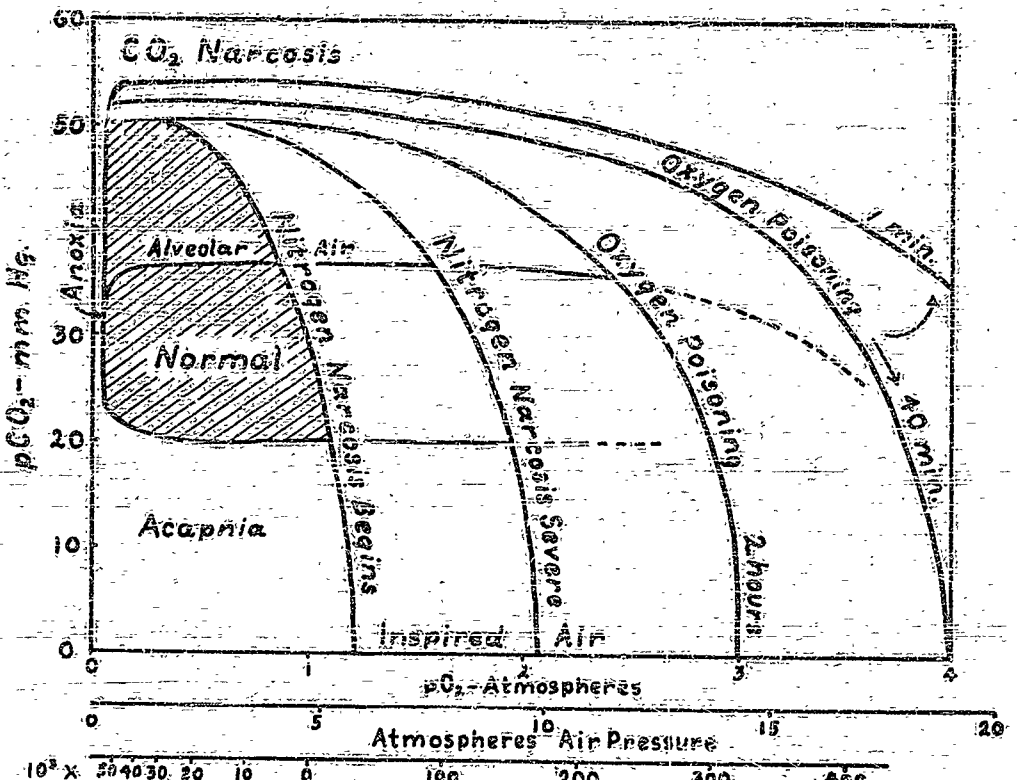

Fig. 10. An alveolar air diagram to illustrate schematically the relation of the normal range of pO_2 and pCO_2 to the abnormal regions characterized by too much or too little of either gas. Abscissae represent oxygen tensions in atmospheres. If these same partial pressures of O_2 are reached by breathing air at pressures indicated on the middle horizontal scale there is the additional complication commonly ascribed to nitrogen poisoning. The lowest scale on the axis of abscissae represents the corresponding altitude in feet breathing O_2 or the depth under water breathing air which would give the same O_2 pressure. Exact positions of the lines are not well established.

result in collapse within a minute as reported by Case and Haldane 1941. Many details of this diagram are still most uncertain as for example the alveolar pCO_2 level at high oxygen pressures and the effect of combining acapnia and high nitrogen or high oxygen. It seems a fair guess that these effects will also be additive so that at high pressures acapnia will occur at higher pCO_2 levels than

under normal conditions. Figure 10 is presented only as a simple means of utilizing this diagram for the demonstration of a large number of physiological effects of respiratory gases.

No originality is claimed for any of the physiological facts reported in this paper. The method of presenting the facts and parts of the mathematical treatment are new and bring out the relationships in a clear and quantitative way which should be helpful in both teaching and research.

SUMMARY

Equations are developed for calculating the alveolar air composition in terms of the altitude, the composition of the inspired air, the alveolar ventilation volume, the rate of oxygen consumption and the R.Q. These equations are illustrated graphically in a series of charts in which pCO_2 is plotted as ordinates against pO_2 as abscissae. The important physiological consequences of these equations are pointed out. The paper represents a theoretical treatment of certain known facts of high altitude physiology.

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A CONCEPT OF MEAN ALVEOLAR AIR AND THE VENTILATION—BLOODFLOW RELATIONSHIPS DURING PULMONARY GAS EXCHANGE

HERMANN RAHN

IN THE past many different methods have been employed for the direct sampling of alveolar air. A sound criticism of the validity of the technique has usually been futile since one was at loss to define or determine mean alveolar composition. The ease with which alveolar air composition can be altered by the slightest change in ventilation is very impressive and makes one aware of the possibility of unequal ventilation in various parts of the lung and the consequential regional variability of gas concentration. The concept of unequal bloodflow to the various alveoli has received less attention, although this factor is equally important in altering the gas composition.

It is the purpose of this paper *1*) to define the alveolar air composition in terms of alveolar ventilation and pulmonary bloodflow which allow one to define a concept of mean alveolar gas composition; *2*) to discuss a method for the direct sampling of mean alveolar air; *3*) to compare this with the Haldane technique of sampling alveolar air; *4*) to predict on the basis of the ventilation-bloodflow equations the effect of unequal ventilation and bloodflow upon the alveolar-arterial oxygen gradient.

A Concept of Mean Alveolar Air. The alveolar air equation and the alveolar ventilation equation have given us a theoretically precise definition of the relation of the alveolar gas concentrations and the ventilation (1). When this equation is combined with the Fick equation, it allows one to express the alveolar gas concentration in terms of bloodflow and ventilation (2).

Let

F = bloodflow in liters/min.
Va = alveolar ventilation in liters/min. B.T.P.S.
$(A\text{-}V)O_2$ = arterial-venous oxygen difference in ml/l.
X_0 = oxygen intake in ml/min. S.T.P.
Q = respiratory quotient
pC = partial pressure of CO_2 in alveolar air.

then the bloodflow according to the equation of Fick is

$$X_0 = F(A\text{-}V)O_2 \qquad (1)$$

and the alveolar ventilation according to Fenn *et al.* (1) is

$$X_0 = \frac{Va \times pC}{.864Q} \qquad (2)$$

Combining the equations and eliminating X_0 we have

$$pC = \frac{F}{Va}(A\text{-}V)O_2(.864Q) \qquad (3)$$

The pO_2 can be calculated for *equation 3* from the alveolar air equation if the R.Q. is known. Since Va and F appear as a ratio, the equation becomes independent of metabolic rate. The pCO_2, pO_2 and R.Q., therefore, become a function of the Va/F for any given inspired gas tension and mixed venous blood gas tension (see below).

The solution of this equation for a given steady state is most easily accomplished by a graphic method. If one assumes a specific pO_2 and pCO_2 tension of the mixed venous blood entering the lung as well as an inspired oxygen tension, then one can graphically, with the aid of the Henderson nomogram for blood and the Fenn diagram (1) for gas R.Q., determine all the simultaneous pO_2 and pCO_2 tensions which satisfy *equation 3*.

This is done in the following manner. Various gas R.Q. lines are plotted radiating from the inspired O_2 tension, I, on the Fenn O_2 CO_2 diagram (fig. 1). The point describing the O_2 and CO_2

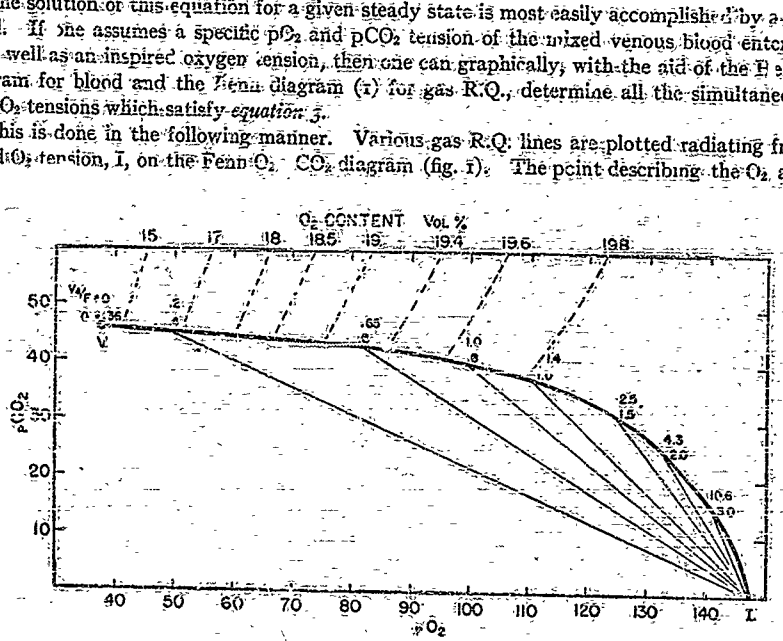

Fig. 1. The curve (solid line) represents all the possible simultaneous O_2 and CO_2 tensions which could theoretically exist in the pulmonary capillaries and the alveolar air when the mixed venous blood has the composition V, and the inspired gas tension has the composition I. The solid diagonals represent various iso-gas R.Q. lines and the dotted lines the iso-oxygen content. Each point on this curve is the product of a certain ventilation-bloodflow ratio, Va/F, which simultaneously determines the respiratory quotient, Q, at which the blood and alveoli are exchanging.

tensions of the mixed venous blood, V, is likewise located on the diagram. A straightedge connecting the venous O_2 and CO_2 tensions of V on the blood nomogram is then pivoted on its point of intersection with a chosen blood R.Q. point until the pCO_2 and pO_2 values correspond to identical values on the diagonal of figure 1 representing the same R.Q. At these tensions only, can blood and alveolar gases exchange at the same R.Q. Similar points can be found for various other R.Q.'s which yield a curve (fig. 1) denoting all the possible combinations of CO_2 and O_2 tensions which could exist under these conditions. Since the original development of this procedure (2) Riley (3) has (personal communication) proposed quite independently a similar solution. Essentially, he plots all the possible O_2 and CO_2 tensions for a given blood R.Q. coming from a given venous point and shows where they intersect the gas R.Q. line. This procedure has much merit for it affords a more graphic visualization of blood and gas exchange on the O_2-CO_2 diagram.

It follows from the equation that any point along this curve is the result of a particular alveolar ventilation to bloodflow ratio, Va/F. To determine this ratio from *equation 3* the (A-V) oxygen difference must be known in addition to the pCO_2 and Q. This can be obtained from the isopleths of arterial O_2 content that have been added to the figure 1. Thus, between the venous point, V, where the ventilation is 0, and the other end of the curve I, where the bloodflow is 0, an infinite number of Va/F ratios can theoretically exist in the various alveoli. In the alveoli where normally the maximal exchange occurs, at an R.Q. of .8, the Va/F ratio in this particular example is 1.0.

We have now defined for this specific example all the possible simultaneous O_2 and CO_2 tensions which could exist in any part of the lung as well as in the pulmonary capillary blood if we assume that the terminal diffusion gradient across the alveolar membrane is for practical purposes negligible. The next object is to determine the *mean alveolar* gas concentration. This is done easily, if the R.Q. is known. Thus, if we choose in our example an R.Q. of .8 then the intersection of this gas R.Q. line with the curve of figure 1 determines the only point at which blood can exchange at this particular R.Q. This is at a pCO_2 and pO_2 of 40 and 100 mm. Hg respectively and assumes that all blood in all the alveoli is exchanging at this particular R.Q. Of course, it is very probable that this is not normally the case and that alveoli exchange individually at various R.Q.'s and that only the mean of all of them result in an R.Q. of .8. As will be discussed below, a normally distributed population of Va/F values will not appreciably affect the predicted alveolar value, but only change the *arterial* pO_2.

The validity of the theoretical alveolar air curve (fig. 1) should be experimentally demonstrable if one could alter the Va/F ratio without changing the steady state and the venous tension, V. The closest approach to such a test can be accomplished by analysis of the alveolar air composition after breath holding and hyperventilation when this is done at various intervals up to one circulation time (20 sec.). It might be assumed that the venous tension will remain constant during this period. Such experiments have been previously described (4), and are here compared with the theoretical curve (fig. 2). Although a discrepancy is apparent, probably due to altered CO_2 output, cardiac output and partial recirculation, a general agreement is rather striking and lends support to the theoretical conclusions regarding the possible combinations of CO_2 and O_2 which could exist simultaneously in the alveoli. It has always been an impressive fact that the simultaneous gas tensions could be altered only along a very narrow and predictable pathway no matter by what method the steady state was altered (5).

Sampling of Mean Alveolar Air. It has been shown above that the mean alveolar air can be theoretically defined provided 3 facts are known: *1)* the venous gas tensions, *2)* the inspired gas tensions and *3)* the R.Q. (It also presupposes that there exists no terminal alveolar membrane gradient.) The question now arises how close these values for the theoretical mean alveolar air can be approached by direct methods which do not involve the sampling of mixed venous blood.

Riley *et al.* (6) have approached this problem by collecting and analyzing the arterial blood for the CO_2 tension. Since such a sample represents a mixture of practically all the blood that has passed through the pulmonary capillaries, it must represent the mean arterial pCO_2 tension and is for all practical purposes in equilibrium with the alveolar pCO_2. (It can be shown that a considerable venous admixture has a negligible effect upon the mean arterial pCO_2 tension. Furthermore, it is shown below that a normal probability distribution of Va/F among the alveoli, likewise has a negligible effect.)

On the basis of the theoretical discussion above, this mean arterial pCO_2 value should be identical with the mean alveolar CO_2 tension. (This theoretical mean tension has been designated as 'ideal' tension by Riley (3)). Thus, substituting mean alveolar CO_2 for mean arterial pCO_2 and determining the respiratory quotient from the expired air, Riley is able to calculate the *mean alveolar* pO_2 from the alveolar air equation. This method is theoretically entirely sound for obtaining the mean alveolar composition but offers practical difficulties since it requires an arterial puncture and considerable skill in the determination of arterial pCO_2. Furthermore, any single determination of arterial pCO_2 by the method of Riley *et al.* (6) can only be read with an accuracy of $\pm$ 3 mm. pCO_2.

On the other hand, methods of obtaining alveolar air directly offer many practical advantages and it is our purpose to ascertain how closely these methods approach the theoretical concept of mean alveolar air. In the past there have been essentially 2 methods of sampling alveolar air. In the original method (Haldane) all the expiratory reserve was forced out of the lung and the last part analyzed, while others have sampled from the last part of each normal tidal volume. These 2 methods do not yield identical results and the difference can probably be best appreciated when the time course of CO_2 concentration is recorded for each individual breath on a fast infrared CO_2 analyzer recently described by Fowler (7) from this laboratory (fig. 3). It can be seen that after the deadspace is washed out with a normal tidal expiration, the CO_2 concentration rises quickly and tends to plateau off. With a forced expiration (Haldane), however, the alveolar CO_2 keeps on rising. This curve is typical of some 15 healthy individuals who have been recorded by this method.

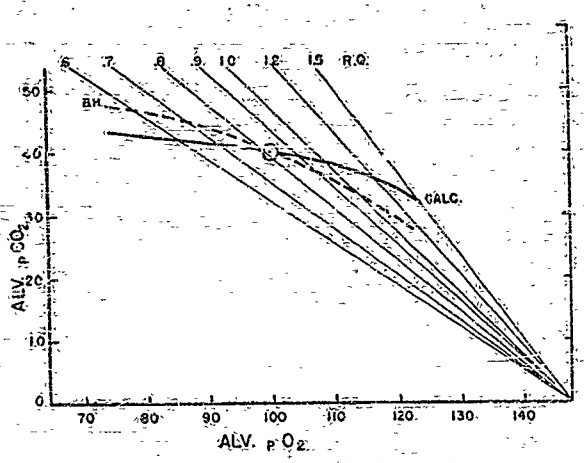

Fig. 2. THEORETICAL ALVEOLAR AIR COMPOSITION CURVE (solid line) compared with directly obtained samples (dashed line) when the V_A/F ratio of the normal alveolar air (open circle) is altered by breath holding or hyperventilation. (see text).

With the Haldane technique part 'X' is sampled. In a method described by us recently (5, 8), part 'Y' is sampled. In this example the CO_2 difference between these 2 points is approximately 3 mm. Hg.

Sampling the last part of each normal tidal has several advantages, for it averages the last 10–15 cc. of each tidal volume expired during normal breathing and, furthermore, it does not require trained subjects for delivering a properly timed, forced expiration. In addition to the automatic sampling the continuous analysis is extremely convenient. In order to determine the reliability of these samples as representing mean alveolar air, tests were performed comparing the alveolar pCO_2 with the arterial pCO_2.

The CO_2 comparisons were carried out by Miss Suskind in this laboratory (unpublished). While the alveolar air was analyzed continuously by the method referred to above, blood samples were taken from the radial artery in the human subjects and the femoral artery in the dogs. This approach allowed for simultaneous sampling of these 2 components. Nine experiments were carried out on man and 80 were done on dogs under nembutal or pentothal narcosis. The mean difference

for all experiments between the alveolar pCO_2 and the arterial pCO_2 was 0.78 mm. Hg, standard error of the mean 0.58. (In our hands we find that on the average the pCO_2 determination of the blood differs from the equilibrating test gas mixture by less than .3 mm. Hg with a standard deviation of 2.5.) These observations would suggest that the alveolar pCO_2 obtained by this method of sampling from the last fraction of each tidal volume is in very close agreement with the arterial pCO_2. Therefore, this value, as pointed out above, represents the mean alveolar pCO_2 unless an appreciable terminal membrane gradient exists, which is unlikely (6).

In the continuous method of alveolar air analysis the pO_2 is simultaneously analyzed and must, therefore, represent the mean alveolar pO_2 provided that the alveolar air R.Q. is identical to the expired air R.Q., the latter representing the classical standard.

To test the possible discrepancy between these, the alveolar R.Q. was determined by continuous alveolar air analysis and compared with R.Q. values from the

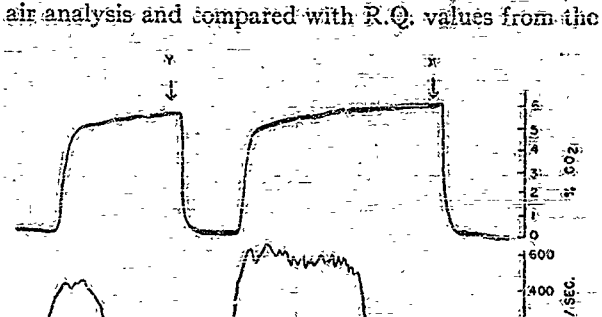

Fig. 3. INSTANTANEOUS CO_2 CONCENTRATION recorded by an infrared analyzer during a normal expiration and a forced expiration. The simultaneous expiratory velocities are recorded below. The inspiratory velocity curve is not shown. X and Y denote the part of the alveolar air sampled by the Haldane technique and the continuous technique, respectively.

collected expired air. The expired air was analyzed by the same automatic meters as well as by Haldane gas analyses in 27 experiments on 7 different subjects. The average values are presented in table 1 *A* and show no significant difference between the expired air and the simultaneous alveolar air R.Q. These results would suggest that this method of sampling yields an R.Q. which is in agreement with expired air R.Q. values. Thus, we may draw the conclusion that the alveolar air sampled continuously from the end of normal tidal expirations, yields a value which must be very close to the theoretical mean alveolar pO_2 and pCO_2.

The other method (Haldane) for sampling alveolar air must also be discussed. This method analyzes the last part of the forced expiration. When this method is compared with samples taken by the previous method (8) one finds on the average a 2 mm. higher CO_2 and a 5 mm. lower pO_2 for the Haldane technique. This is not surprising when we look at figure 2 and also consider that this forced expiration usually lasts 2–3 seconds beyond the time taken for a normal expiration (end-expiratory sample). Similar differences were obtained by Riley *et al.* (6) who compared the alveolar CO_2 obtained by the Haldane technique (end-inspiratory samples) with the arterial pCO_2. They observed on the average a 4.4 mm. Hg higher value in the alveolar sample taken at rest.

It should be pointed out that the subjective impression of the time it takes to expire completely may be quite misleading, unless a simultaneous air velocity record is obtained. It is during the last phase of expiration that the CO_2 in many subjects rises rather steeply due to the smaller lung volume which is still exchanging with the blood. Actually, tests have shown (unpublished) that during this prolonged expiration, the oxygen uptake remains normal, but the CO_2 output is reduced. The net result is that not only must the CO_2 rise above and the O_2 fall below the average value existing at the end of a normal tidal, but the ratio between oxygen uptake and CO_2 output is altered, producing an abnormally low R.Q. These changes become exaggerated when larger intervals than 2–3 seconds are used for the forced expiration or when the breath is held (4).

Table 1 *B* shows the alveolar R.Q. differences obtained by the 2 methods of sampling. These experiments were done on 10 subjects and were reported elsewhere (8). But in view of the values cited in table 1 *A*, they assume new interest

TABLE 1

A

COMPARISON OF EXPIRED AIR R.Q. AND ALVEOLAR AIR R.Q. (END OF NORMAL TIDAL SAMPLE)

	Mean R.Q.	S.E.M.	n
Expired air R.Q.	.828	.010	27
Alveolar air R.Q.	.829	.007	27
Δ	.001		

B

ALVEOLAR R.Q. OBTAINED BY SAMPLES FROM:

	R.Q.	S.E.M.	n
End of normal tidal expiration	.821	.0052	148
End of forced expiration	.790	.0054	148
Δ	.031		

since they show the Haldane method to deviate from the expired air R.Q. and by an average value of .03 R.Q. units. This would support the contention that a forced expiration is actually equivalent to breath holding which brings about similar changes in O_2, CO_2 and R.Q. of alveolar air (4).

The O_2 and CO_2 Dead Space. The discrepancy between the tidal air samples and forced expiration samples, furthermore, explains the difference which has been noted by others between the dead space calculated from the oxygen values and CO_2 values. Theoretically, it can be shown that this dead space must be the same as long as the R.Q. of the expired and alveolar air are the same. The reason for the observed difference of a larger oxygen dead space is very probably that the alveolar samples were always obtained by the Haldane technique. Figure 4 shows the average expired air, E, and the alveolar air, A, values obtained in 27 experiments in which the alveolar CO_2, O_2 and R.Q. values were 38.1, 102 and .829 and the expired CO_2, O_2 and R.Q. were 27.8, 114 and .828 respectively. The Bohr formula, $\frac{\text{deadspace}}{\text{tidal volume}} = \frac{A-E}{A}$ can be represented graphically in figure 4 for the O_2 as well as the CO_2 values. The ratio $\frac{A-E}{A}$ must be equal for both sides of the quadrangle as long as both A and E are on the same diagonal or R.Q. line.

If one assumes on the basis of the former experiments (6) that a Haldane sample had been delivered instead, the alveolar air values would have been located at point A-1 in figure 4. During the delivery of the sample, the concentration of point A would change and move up on the breath-holding curve, B.H. (4).

The actual values cited above yield with the average tidal volume of 648 cc. (B.T.P.S.) an O_2 and CO_2 deadspace of 176 cc. If we subtract a 35 cc. apparatus deadspace from this figure, we obtain a personal deadspace (breathing through the nose) of 140 cc. Had Haldane samples been used instead, the personal deadspace

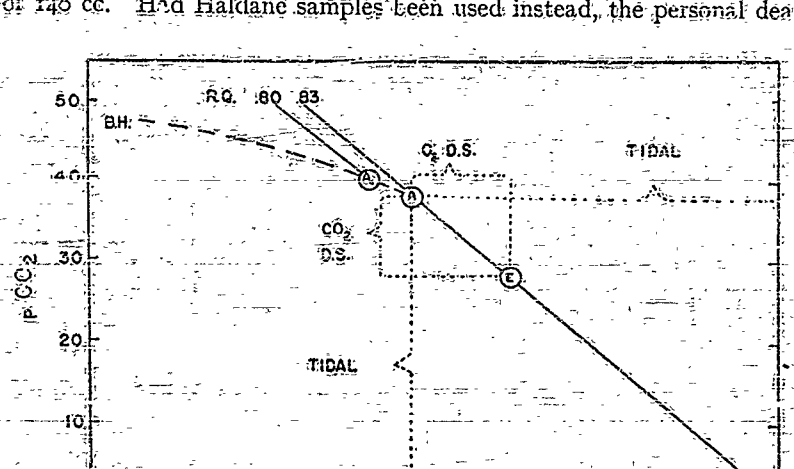

Fig. 4. A AND E REPRESENT the average alveolar and expired gas concentrations which fall upon the same R.Q. diagonal. The relative dead space to tidal volume ratio is shown graphicaly for O_2 and CO_2 and are the same as long as the R.Q. for E and A are the same. Point A-1 represents the alveolar value which would have resulted if the sample had been delivered from a forced expiration instead of from the end of a normal tidal expiration. The broken curve, B.H., describes the alveolar air changes when the breath is held at A (see text).

would have been 164 cc. for CO_2 and 188 cc. for O_2. On the basis of the foregoing discussion it would appear that the deadspace values derived from Haldane samples are probably too large, particularly for the O_2 deadspace.

Effect of Unequal Ventilation and Bloodflow upon the Alveolar-Arterial Gradient. In the foregoing discussion the concept of the theoretical mean alveolar gas concentration was based upon the assumption that all alveoli exchanged at the same R.Q. However, there is much evidence that ventilation is not equal in various parts of the lung (for a recent review see Rauwerda (9)) and Wearn *et al.* (10) have shown that the bloodflow is not constant in the alveoli. Thus, to appraise the variations in gas concentrations that may exist from one alveolus to the next and what effect this would produce upon the mean alveolar gas composition as well as upon the mean arterial gas tension, the variation of bloodflow and alveolar ventilation must be considered. Since both exert their effect upon the gas tensions, it is convenient to con-

sider them simultaneously and to evaluate the effect of the variation of alveolar ventilation to bloodflow ratio, Va/F (1.1). From *equation 3* we obtain by rearrangement:

$$\frac{Va}{F} = \frac{.864\ Q\ (A\text{-}V)O_2}{pC} \qquad (4)$$

If we return to our original conditions of our example, figure 1, with a R.Q. equal to .8 then the mean alveolar pO_2 and pCO_2 must be 100 and 40 mm. Hg respectively, provided all the blood in all the alveoli is exchanging at this R.Q. Furthermore, these particular tensions are brought about by a Va/F ratio of 1.0.

Theoretically other Va/F ratios can occur ranging from 0 at the venous point to ∞ at the inspired gas tension. Therefore, we may assume that the distribution of

TABLE 2

A) Values which will be found at the various standards of deviation which are not apparent in fig. 4

	−3	−2	−1	MEAN	+1	+2	+3
Va/F	.45	.59	.77	1.00	1.30	1.69	2.20
R.Q.	.73	.66	.68	.80	.98	1.17	1.38

B) Blood and alveolar values which would be obtained if all alveoli exchanged at a Va/F ratio of 1.0, (A), are compared with the mixture which would result if the Va/F ratio varied around the mean (B) (see text)

	O_2 CONTENT	CO_2 CONTENT	ALV. pO_2	ALV. pCO_2
A	19.65	48.00	100	40
B	19.55	47.90	99.4	39.7
Difference	0.10	0.10	0.6	0.3

the pulmonary bloodflow, F, as well as the ventilation, Va, among the various alveoli is normal along a logarithmic scale.[2] The distribution of the ratio Va/F will then also be normal along a logarithmic scale. Returning to our example, we can say that not all alveoli have a Va/F of 1.0 but that some have a larger and others a smaller ratio distributed along a normal logarithmic distribution curve with the mean of the log 1.0. A standard deviation equal to the log 1.3 is arbitrarily chosen.

Table 2 *A* lists the various Va/F ratios and R.Q.'s which then will be found at 1, 2, and 3 standard deviations from the mean Va/F of 1.0 and figure 5 shows how this distribution affects the O_2 and CO_2 content of the arterial blood and the pO_2 and pCO_2 of the alveolar air. The resulting mixtures which would result for each of the 4 entities are calculated (the sum of the values of each class interval multiplied by the frequency of its occurrence) and listed in table 2 *B* to be compared with the theoretical mean value which would be obtained if no variation of Va/F had oc-

[2] Among the various kinds of distribution curves, this is probably the simplest form which could be assumed for the distribution of a ratio.

curred as originally assumed. It can be seen that from a practical standpoint none of the resulting mixtures differ from the theoretical mean with the exception of the O_2 content. Here we find that the arterial blood leaving the lung capillaries has an O_2 content 0.1 volume per cent lower than if all the exchange had gone on at a Va/F of 1.0. The arterial blood leaving the capillaries is, therefore, represented by the open circle (fig. 5) and it can be seen that this is at an oxygen tension 8 mm. Hg lower than the mean alveolar O_2 tension. (Although the CO_2 content of the mixture also differs from the theoretical value by the same amount as the O_2 content, it affects the arterial pCO_2 by less than 0.2 mm. Hg.) It should be pointed out that the

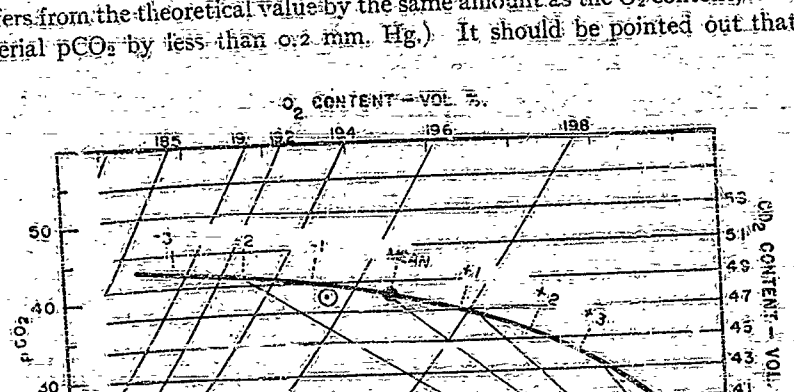

Fig. 5. DISTRIBUTION OF THE PULMONARY blood gas values and alveolar gas values when a normal logarithmic distribution of Va/F is assumed around the mean value (solid circle). The resulting average mixture of the arterial blood will be altered only in respect to the oxygen content and arterial pO_2 (open circle). The resulting average mixture of alveolar gases remains essentially unchanged. Thus, the distribution of Va/F induces an alveolar-arterial pO_2 gradient of 8 mm. Hg (see text).

mixed alveolar air as well as the mixed arterial blood points (table 2, *B*) no longer lie precisely on the blood R.Q. or gas R.Q. line of .8. This would suggest that the Va/F ratios are not symmetrically, but unequally distributed in such a manner that the mixed values still maintain an R.Q. of .8. However, the above example is a first approximation and the discrepancy in this case may be considered negligible.

When, under otherwise identical conditions, various other venous points are chosen, the pO_2 gradient is not appreciably altered. This means that a large or a small $(A\text{-}V)O_2$ difference does not affect this gradient. On the other hand, if a larger deviation of Va/F than log. 1.3 is assumed, the pO_2 gradient can become appreciably larger. This may explain the greater alveolar-arterial oxygen gradient observed during exercise by Riley *et al.* (6). It should also be pointed out that an unequal distribution of Va/F ratios will result in increased O_2 gradients, particularly if a preponderance of alveoli have a Va/F ratio which is smaller than the theoretical mean.

As discussed before, the standard deviation of this ratio was quite aribtarily chosen and at present there is no way to ascertain the magnitude of this deviation nor whether the distribution of this Va/F ratio is distributed symetrically or asymetrically. On the other hand, with the above assumption we can say that in the normal lung this deviation is no greater than the one we assumed because the gradient of 8 mm. pO_2 obtained is of the same order of magnitude as that observed for the total gradient normally occurring (6). This gradient has so far been largely attributed to venous admixture arising from direct venous shunts, Thebesian and bronchial veins.

SUMMARY

An equation is derived which expresses the alveolar gas concentration in terms of the relative alveolar ventilation and pulmonary bloodflow. A graphical solution of this relationship is given which describes all the simultaneous O_2 and CO_2 concentrations which could theoretically exist for given mixed venous and inspired air tensions of these gases. Each of the possible alveolar air values, and therefore each R.Q., is determined by a definite ventilation to bloodflow ratio. If the R.Q. is known, the theoretical mean alveolar air composition can be defined by this equation.

This theoretical concept of mean alveolar air presupposes that the ventilation to bloodflow ratio is the same in all the alveoli. Since this is unlikely, a variation of this ratio along a normal distribution curve is assumed. The mean alveolar air mixture resulting from such a distribution does not differ appreciably from the theoretical mean. The resulting arterial blood mixture, however, yields a lower pO_2 tension, thus giving rise to an alveolar-arterial oxygen gradient.

Evidence is presented which indicates that the sampling of alveolar air from the last part of each normal expiration yields a value which is very close to the theoretical mean alveolar air composition, while the Haldane method of sampling yields CO_2 values which are slightly too high and R.Q. values which are slightly too low. The latter method is responsible for the difference in dead space volumes when they are calculated separately from the O_2 and CO_2 values. Theoretically, the volumes should be the same if the expired air R.Q. and alveolar air R.Q. are equal.

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HYPERVENTILATION AND THE TRANSPORT OF OXYGEN

by

Wallace O. Fenn, Hermann Rahn, and Leigh E. Chadwick

Some degree of hyperventilation is the normal response to exposure to high altitudes. Presumably this is beneficial or it would not occur so regularly. It represents a more advantageous division of the available pressure between oxygen and carbon dioxide. When the pCO_2 is diminished by hyperventilation, there is a corresponding increase in pO_2. If the R. Q. is 1.0 or if the inspired mixture is pure oxygen then any loss of CO_2 provides an equal increment in O_2. Unquestionably, the arterial saturation at altitudes can be increased by hyperventilation. (Fenn et al, 1949). There is danger, however, that the hypocapnia by its adverse effect on performance (Rahn et al. 1946) may more than offset the advantage of this increased saturation. In addition, it is often argued that low CO_2 is disadvantageous because of the Bohr effect. While a low CO_2 may increase the loading of oxygen in the lungs, it will likewise hinder the unloading at the tissues. This paper is concerned with the theoretical aspects of this problem.

The tension of oxygen in the alveoli represents the total head of oxygen pressure which is available for diffusion in the pulmonary and the tissue capillaries. If the diffusing surface is diminished in the lungs more of this total head of pressure will be devoted to pulmonary diffusion and there will be less left over for diffusion in the tissues. The difference between the alveolar tension and the mean oxygen tension in the pulmonary capillaries is the pulmonary gradient.

The mean oxygen tension in the tissue capillaries represents the maximum head of pressure which is available for diffusion into the tissues. If this is decreased below a certain minimum value the amount of oxygen which can be discharged in the tissues may be inadequate for the metabolic demands of the tissues. A level of 20 mm Hg is often taken as the minimum venous oxygen tension which is consistent with the needs of the tissues. The venous level is, of course, always somewhat below the mean tissue capillary tension but the venous pO_2 may be taken as a convenient indication of the pressure head available in the tissue. The difference between the mean tensions of oxygen in the tissue and lung capillaries represents the pressure head which is not used anywhere for diffusion but is in effect "wasted in the circulation".

With these considerations in mind, the problem of determining the optimum pCO_2 for oxygen transport resolves itself into a determination of the cardiac output which would be needed to produce a given venous oxygen tension at different arterial levels of carbon dioxide and oxygen. This can best be done graphically on an oxygen-carbon dioxide diagram as described by Fenn et al (1946). On such a diagram the partial pressures of oxygen are plotted as abscissae and partial pres-

sures of CO_2 as ordinates. The CO_2 contents of the blood (in cc per 100 cc. of blood) are then represented by a series of horizontal lines (Fig. 1) which bend down slightly at low partial pressures of oxygen. This is due to the fact that at low oxygen pressures less partial pressures of CO_2 is required for the same CO_2 content. The oxygen contents of the blood are similarly represented on the same chart by another family of lines curving upward to the right. As the pCO_2 increases, a greater pO_2 is required for the same saturation because of the Bohr effect.

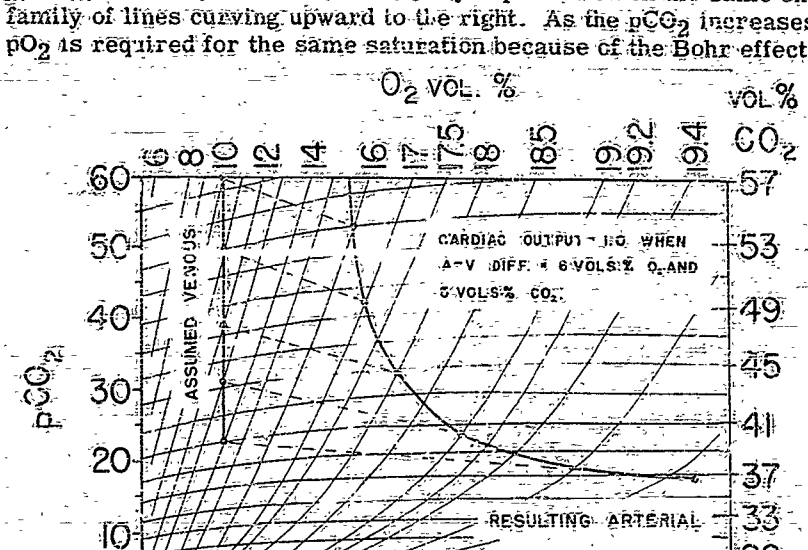

Figure 1

The vertical line in Fig. 1 represents an assumed minimum venous pO_2 of 30 mm which will satisfy the demands of the tissues. Assume now a cardiac output and gas exchange such that the arterial-venous difference is 6 vols. percent for O_2 and 5 vols. percent for CO_2. Then for each point on the assumed venous pO_2 line it is possible to pick a corresponding point on the chart where the oxygen content is 6 vols. percent greater and the carbon dioxide content is 5 vols. percent less. Five such pairs of points have been connected in Fig. 1 by dotted lines. The heavy line joining these points represents the arterial points which will just give a venous pO_2 of 30 mm. at the assumed cardiac output. Similar curves can be constructed for a cardiac output which is 120%, 150%, 200%, etc. of the originally assumed value. A family of such cardiac output curves has been indicated in Fig. 2.

Similarly, it is possible to start with other assumed venous pO_2 values greater or less than 30 mm. and draw the arterial lines for a cardiac output of 100%, i.e. a cardiac output which would give A-V differences of 5 and 6 vols. percent for CO_2 and O_2 respectively. This has been done in Fig. 3 where the heavy lines represent another such family of curves, each for a different minimum venous pO_2 value.

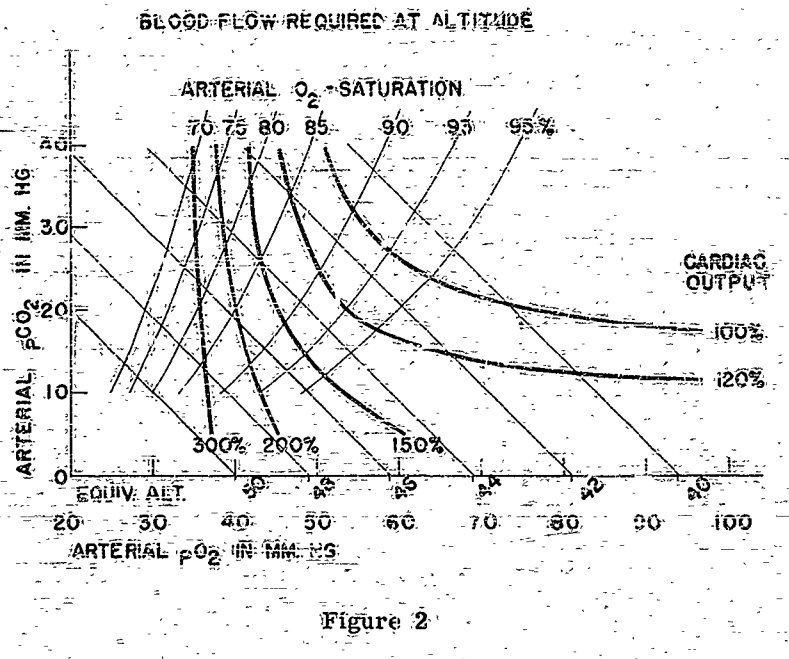

Figure 2

The significance of these charts may now be considered. In Figs. 2 and 3, in addition to the two families of curves already mentioned, there is a series of straight diagonal lines sloping downward to the right at an angle of 45 degrees. These are altitude diagonals (for 100% O_2 or R. Q. = 1.0) each one representing a given barometric pressure. Along such a line the sum of the partial pressures of CO_2 and O_2 must be a constant and equal to B-47 for that altitude. In Fig. 2 we may start at a normal alveolar partial pressure of CO_2 of 40 mm. at an altitude of 42,000 ft. As the ventilation is increased the pCO_2 will decrease and the alveolar point will move downward to the right along the 42,000 ft altitude diagonal. In so doing the oxygen saturation and the pO_2 increase. At the same time the curvature of the cardiac output lines is such that the alveolar point moves further away from the 120 cardiac output line and closer to the 100% cardiac output line. This means that by overventilating the venous pO_2 of 30 mm can be maintained with a smaller cardiac output than would be required at an alveolar pCO_2 of 40 mm. After passing the 93% oxygen saturation line it is evident that any further decrease in pCO_2 will bring the alveolar point closer to the 120% cardiac output line. From this point on, therefore, a further lowering of the pCO_2 becomes disadvantageous from the point of view of oxygen transport. The 93% oxygen saturation line passes close to the point of maximum curvature of the cardiac output lines, i. e. the point where they reach or become tangent to the highest altitude diagonal. This justifies, therefore, the general statement that for purposes of oxygen transport an increase in ventilation is beneficial provided it does not increase the percentage oxygen saturation of the blood above 93%.

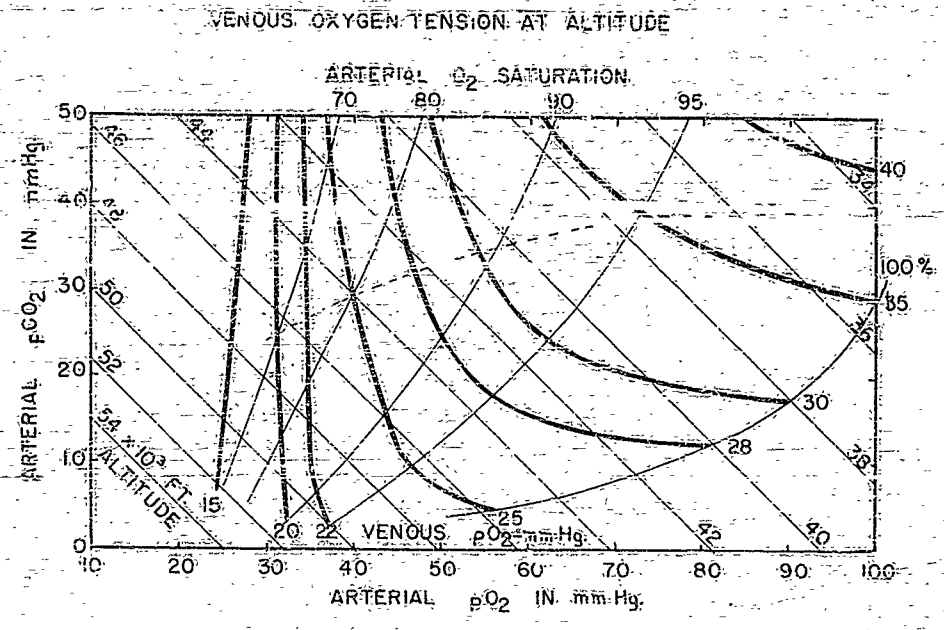

Figure 3

The chart in Fig. 3 can be analyzed in a similar manner. In this case, starting as before at pCO_2 of 40 mm and an altitude diagonal of 42,000 ft., it will be seen that an increase in ventilation lowers the pCO_2 along the altitude diagonal and brings the alveolar point closer to the venous pO_2 curve for 30 mm and further from the venous pO_2 curve of 28 mm. This means that an increase in ventilation will increase the venous pO_2 without any change in the cardiac output. In Fig. 3 it is the 95% oxygen saturation line which passes through the points of maximum curvature of the heavy venous pO_2 lines, although the 93% saturation line would follow this rule almost as well. In Fig. 3 the normal alveolar pCO_2 at different altitudes is represented by a dotted line across the middle of the chart. It can be seen that this curve lies above the 95% oxygen saturation line at all altitudes above 38,000 ft., or at all altitudes where pure oxygen at ambient pressure becomes insufficient and the ventilation is increased. This justifies, therefore, the statement that, in general, a subject at altitude would improve his oxygen transport if he increased his ventilation somewhat more than his respiratory center would seem to "advise". It should be emphasized, however, that this statement applies only to the function of oxygen transport. It does not state that the subject as a whole would be better off with more ventilation. For a broader generalization of this sort it would be necessary to consider the effects of hypocapnia on the neuromuscular coordination and general performance of the subject. (Otis, Rahn et al, 1946). On this basis the argument in favor of hyperventilation is less strong. Our present purpose is merely to point out that hyperventilation at altitude should not be feared because of its effect upon the transport and particularly because of interference with the unloading of oxygen at the tissues.

DISCUSSION

Evidence has been presented to show that under conditions of hypoxia hypocapnia does not interfere with the transport of oxygen. The increase in saturation of the arterial blood which occurs in overventilation is an advantage which overbalances the difficulty in unloading oxygen in the tissues when the CO_2 tension is low. There is little further gain in the lungs, however, after the arterial blood has reached a saturation of 93 or 95% and beyond this point increasing the ventilation further is more of a disadvantage than an advantage.

From the point of view of general performance it is true that low pCO_2 is disadvantageous but the change is minimal until the alveolar CO_2 tension is decreased to 20 or 25 mm. For this reason we have felt that for most men there is more danger of underventilating at altitude than of overventilating. Our performance tests seem to have borne out this opinion. (Rahn, Otis, et al 1946).

If hyperventilation is advantageous at altitude then, conversely, it might be expected that the addition of CO_2 to the inspired air would be disadvantageous. In spite of some contrary evidence this seems to be true (Otis et al 1949) so long as the CO_2 is added to pure oxygen for use at altitude. In that case the ventilation is increased until the alveolar pCO_2 is scarcely greater than normal and the alveolar pO_2 is consequently unchanged. The subject merely has to breathe harder to maintain the same mixture of gases in his alveoli.

When CO_2 is added to air for use at altitude, the situation is very different for reasons which have already been pointed out by many workers. (cf Fenn et al 1946). Briefly, the ventilation is increased so that less oxygen is taken out of each liter of air inspired; the alveolar pO_2, therefore, increases with corresponding improvement in performance. An experimental study of this situation has been offered by Rahn and Otis (1949). Here CO_2 is advantageous because it permits a high ventilation without corresponding diminution of alveolar CO_2. It should be noted, however, that a mere rise in alveolar pCO_2 without change in oxygen is disadvantageous while loss of CO_2, within the limits defined in this paper, is in general advantageous. This seems to be true provided the saturation of the arterial blood does not exceed 93% and provided the alveolar pCO_2 does not fall below 25 mm.

SUMMARY

The advantage of hyperventilation at altitude depends upon a balance between the beneficial effect of low CO_2 in facilitating the uptake of oxygen in the lungs and the disadvantageous effect of low CO_2 in hindering the unloading of oxygen in the tissues.

From the published data on the CO_2 and O_2 contents of human blood at different tensions of these gases it is concluded that in subjects at altitude, hyperventilation is beneficial for the transport of oxygen to the tissues so long as the oxygen saturation is less than about 93%.

The discussion concerns only the transport of oxygen and not the general condition of the subject who may be significantly deteriorated by the acapnia if the pCO_2 is less than 25 mm.

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PHYSIOLOGY OF EXPOSURES TO ABNORMAL CONCENTRATIONS OF THE RESPIRATORY GASES

WALLACE O. FENN

I HAVE had the temerity to select the whole broad field of the physiology of the respiratory gases for my subject but obviously there are only certain limited aspects with which I shall be able to deal. My particular purpose is to make use of a new type of diagram for the illustration and analysis of certain problems of respiration. This particular method of plotting data has proved itself exceedingly useful in our laboratory for the understanding of the rather complicated mathematical process of the regulation of the alveolar air of the lungs by the breathing. I shall try to show you how useful this chart is and to point out the reasons why it is better for this purpose than are other more familiar methods of plotting. Incidentally I may be able to describe to you in terms of this chart the results of some of our various experiments in the field of respiration.

The chart in question represents carbon dioxide and oxygen pressures in the alveolar air as ordinates and abscissae respectively. Such a chart, as shown in figure 1, gives a bird's eye view of the field of respiratory gases. Any combination of concentrations of these gases can be represented by a suitable point on the chart, and any respiratory experiment involving changes in the concentrations of these gases can be represented by a line. Man is adapted to function normally over a rather small range as indicated in the center of the chart. Outside of this central region is another area within which consciousness is generally retained but not without serious deterioration of the performance, especially near the borders. Anywhere outside of this second area consciousness is quickly lost and convulsions or death occur regardless of the cause. This might indicate that in all cases the final cause of loss of consciousness was the same—possibly lack of oxygen in the brain. This might occur either because of lack of oxygen in the air or because of a defective circulation to the brain as a secondary result.

The dangers of high CO_2 might occur by breathing too slowly, by obstruction of the trachea or drowning or by breathing in a closed space. If the CO_2 tension becomes higher than 10 per cent consciousness is lost in ten minutes or less, for CO_2 has a narcotic effect in high concentrations (Seevers, 1944). On the contrary too much ventilation of the lungs leads to acapnia or lack of CO_2. The symptoms of acapnia are tingling in the fingers, toes, or the whole body, twitching in the face, muscular incoordination, a feeling of lightheadedness, and finally muscular spasms or tetany.

On the summit of Mt. Everest or in an airplane at a sufficient altitude the lack of oxygen results in collapse from anoxia. This can hardly occur from rebreathing in a closed space unless the volume of that space is as small as about 100 liters because in larger volumes the carbon dioxide reaches toxic levels before the oxygen can be dangerously reduced. In small volumes sufficient CO_2 can be retained by the alkaline reserve of the body so that oxygen depletion can proceed to lethal limits.

While we die quickly without sufficient oxygen, the chart shows that we can also have too much of a good thing because in deep diving operations oxygen poisoning is a familiar hazard and accounts for many cases of erratic behavior of men working under water at great depths. In 1938 I had the thrill of reading Commander Ellsberg's account of his underwater enterprises entitled *Men Under the Sea*. I was somewhat skeptical when I read (p. 124) that in the high oxygen pressure of the compressed air which the diver required on the bottom "the fat of his body is literally burned out of him after a few deep dives." While this expression presumably was not intended to be a scientific statement of fact it nevertheless set me to wondering what the effect would

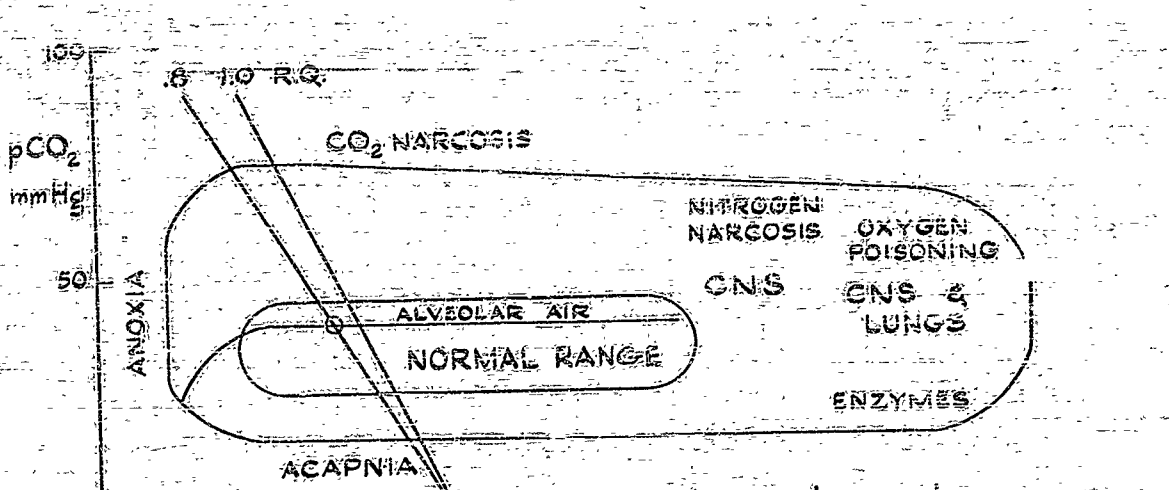

FIG. 1. Diagram to illustrate approximately the normal and abnormal ranges of CO_2 and O_2 concentrations in the alveolar air in the lungs.

really be on the rate of oxygen consumption of tissue if the oxygen pressure were increased. The natural inference of course is that the rate of burning would be increased but experiment showed that just the reverse was actually true.

Oxygen consumption is usually measured either by pressure or volume in a small glass vessel or respirometer but this technique is difficult at high pressures. We accordingly planned to measure the rate of CO_2 output as an indication of metabolic rate. This was done by absorbing the carbon dioxide in a solution of barium hydrate and measuring its electrical conductivity. This apparatus, containing a bit of muscle or kidney or skin of a frog, was enclosed in a heavy bomb, built to stand 50 to 60 atmospheres of pressure. With the help of Miss Elizabeth Cass, now of Russell Sage College, a series of measurements was made which showed that, after a brief initial increase, the CO_2 output was diminished when the oxygen pressure was increased. The higher the pressure the lower the final level. When the oxygen pressure was returned to normal the rate of metabolism of the tissue increased again. The same pressure change caused by nitrogen did not have this effect. Before these results were published (Cass, 1947), the same finding was reported by Dr. Stadie (1945) of this city. The chain of reactions involved in the oxidation of foodstuffs evidently functions properly only at certain intermediate pressures of oxygen. Whether this inhibition of the enzymes which occurs at high oxygen pressures causes the central nervous system symptoms and the edema of the lungs which seems to be the immediate cause of death in oxygen poisoning, is a debatable question because we do not know whether these effects occur *in vivo* soon enough and at a low enough pressure to explain the symptoms.

Nitrogen poisoning is a less well defined entity, but a definite deterioration in the mental activity and performance of divers has been reported by Behnke (1935) and by J. B. S. Haldane (with Case, 1941) and their colleagues. The reports demonstrate convincingly that we are dealing with a real phenomenon. It occurs at oxygen pressures too low to cause oxygen poisoning. It is not due to pressure *per se* because it does not occur in a similar pressure of helium. The result is generally interpreted in terms of the lipoid solubility of the nitrogen. When the pressure is sufficient to force the necessary number of nitrogen molecules into solution in the lipoid layers of the brain cells, narcosis appears as with any other narcotic in spite of the chemical inertness of this molecule. During the past year Dr. Charlotte Haywood has been looking for this phenomenon of nitrogen narcosis in simpler systems such as white blood corpuscles phagocytizing starch grains, and isolated nerves responding to electrical stimulation but we have unfortunately not yet

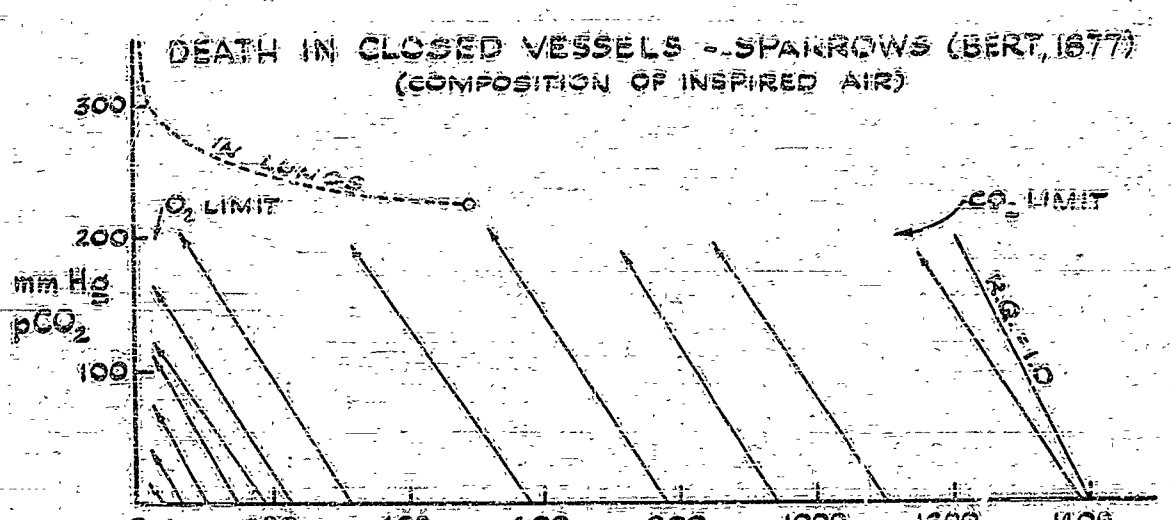

FIG. 2. Arrows indicate changes in pressure of CO_2 and O_2 in the gas in a closed vessel in which a sparrow is confined. The tip of the arrow marks the death of the sparrow.

been able to establish any effect of the nitrogen with certainty. Close observations of the behavior of the microscopic crustacean *Daphnia* when exposed to these pressures of 800 lbs. of nitrogen did not reveal any definite effects. These experiments are continuing and we have hopes now of finding some positive effects but the recent experiments are too preliminary to warrant their mention at this time.

It is noteworthy that the effects of high CO_2 are additive to the effects of both high and low O_2 as indicated by the rounded corners of the areas outlined in figure 1. The effects of low CO_2 are also additive to the effects of low O_2; probably low CO_2 effects are additive to those of high O_2 but this is purely guesswork at the present time.

Through the area on the chart which represents the normal range there runs the alveolar air line which represents the normal level of carbon dioxide in the air deep inside the lungs as a function of barometric pressure or altitude. The normal alveolar point, marked by a circle, lies on a diagonal coming from a point on the base line which represents the composition of the inspired air at ground level with $pO_2 = 149$ and pCO_2 practically zero. If, in the lungs, oxygen is removed from this air and carbon dioxide is added in exactly equal amounts its composition will change along the line marked R.Q. = 1.0.[2] In the normal metabolism of the body, however, the CO_2 output is only 80 or 85 per cent of the oxygen consumed. We can imagine therefore that as the inspired air is taken into the lungs it is "processed" by loss of O_2 and gain of CO_2 in such proportions that its composition changes along the line marked R.Q. = 0.8 until it reaches the alveolar point. Actually when we inspire the alveolar air is slightly diluted so that the alveolar point moves slightly down the 0.8 diagonal and then returns to the normal value before the next inspiration.

The alveolar air line is nearer the top of the normal range than the bottom and this is significant of one dominant fact in the control of respiration. When the CO_2 goes slightly above the alveolar air line it stimulates an overpowering urge to breathe. Breathing dilutes the alveolar air and lowers the pCO_2 to the normal value. On the other hand if one grows excited and breathes abnormally deeply and frequently, as some aviators have done under combat conditions, the alveolar point moves down the diagonal toward the region of acapnia without however provoking any inhibitory sensation. The control of respiration

[2] R.Q. or sometimes Q is the abbreviation for respiratory quotient, this being the ratio of the CO_2 given out to the O_2 taken in.

is therefore a balance between an unconscious desire to breathe as little as possible and a definite stimulus which is aroused when CO_2 is too high or the O_2 is too low. The stimulus due to low O_2 is responsible for the way in which the alveolar air line dips down as the oxygen tension falls below 60 mm Hg or as the altitude increases above 18,000 feet.

The oxygen-carbon dioxide diagram serves well to illustrate some pioneer experiments of the French physiologist Paul Bert published in 1878. These are described in his famous book on *Barometric Pressure* in the chapter entitled "Death in Closed Vessels." The experiments were simple and involved placing sparrows under bell jars at different pressures and with different amounts of oxygen added to the air. After closing the chamber the sparrow used oxygen and gave off CO_2 in accordance with the metabolic R.Q. (or CO_2/O_2 ratio) until eventually the carbon dioxide concentration became so high or the oxygen concentration so low that death ensued. When the animal died a sample of the air was taken and analyzed. In the chart (fig. 2) each diagonal line represents the changing composition of the air produced by one bird, starting at the base line and proceeding upwards to the left to the point of the arrow where breathing stopped. Thereafter the air in the bell jar suffered no further change but the air in the lungs rapidly lost its remaining oxygen and gained CO_2 (as indicated by the dotted line drawn for one of the cases) until the heart also stopped and death ensued a minute or too later. It can readily be seen that at initial oxygen pressures below 200 mm, the bird died when the oxygen pressure of the inspired air diminished to about 25 mm Hg. At pressures above 200 mm on the other hand the carbon dioxide reached a lethal concentration of about 200 mm before the oxygen could be depleted to lethal levels. Why sparrows can tolerate 200 mm of CO_2 while man loses consciousness at 70 or 80 mm in ten minutes or less we cannot say. Note that in the sparrow as in man the slope of these lines is less than the slope of 1.0 at which the loss of O_2 and the gain of CO_2 are equal.

The survival period in a closed vessel naturally depends upon the size of the vessel. If a man were sealed up hermetically in the Grand Central Station it would require about twenty years before the CO_2 level reached a value of 10 per cent (if I have guessed the size of the station correctly).

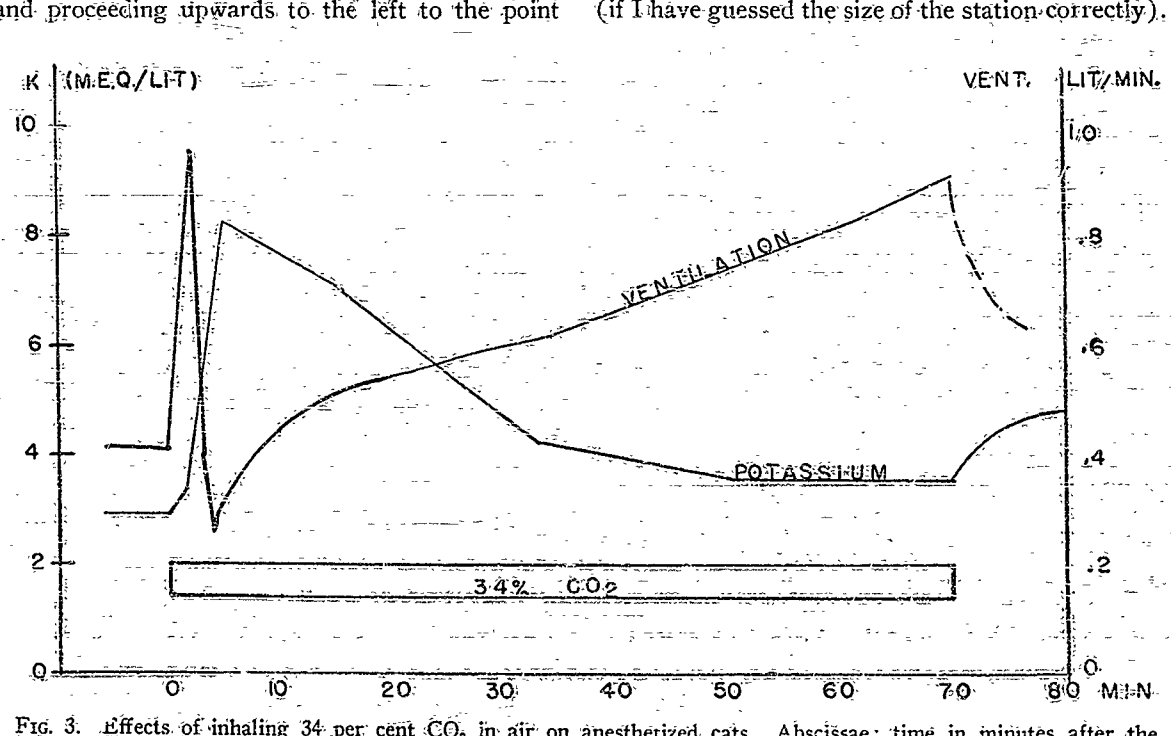

FIG. 3. Effects of inhaling 34 per cent CO_2 in air on anesthetized cats. Abscissae: time in minutes after the beginning of the CO_2 period. Ordinates: concentration of potassium in the blood plasma in m.eq. per liter (left) and pulmonary ventilation in lit. per minute (right).

If this concentration were reached quickly it would cause unconsciousness in about ten minutes. With twenty years for adaptation a man might tolerate a far higher concentration. In our laboratory Dr. Otis and Mr. Chapin spent three days in a gas tight room in an atmosphere of 3 per cent CO_2 and developed a definite decrease in their sensitivity to carbon dioxide as judged by their rate of ventilation and alveolar carbon dioxide tension. Similarly two dogs were kept in this room for two weeks in a concentration of carbon dioxide which rose gradually to 11 per cent. In this time the adaptation which they showed was not sufficient to permit any further increase in the level of CO_2. They lost all appetite for food and were definitely morbid but recovered promptly when they were restored to normal conditions. A considerably longer time would presumably be required for significant further adaptation. Seevers (1944) however has raised rats in increasing concentrations of CO_2 until some of them were able to withstand 20–25 per cent for twenty-nine days but not without the loss of half the body weight.

Acute exposure to very high carbon dioxide tensions of 30 or 40 per cent provides good surgical anesthesia for some animals like rats but in man there is said to be too much tendency to cause convulsions. Recovery from such CO_2 narcosis is prompt. An acute exposure to concentrations of this order has far reaching effects on the physiology of the animal and results in death if continued for several hours. The blood pressure rises rapidly and then falls and a heart block may develop. The breathing is also first stimulated and then depressed. This may be illustrated by some experiments of Miss Joanna Mackay (1947) on anesthetized cats exposed to 34 per cent CO_2, and illustrated in figure 3. The graph shows that in addition to the transitory increase in the breathing there is a sudden escape of potassium from the tissues into the blood. In the course of half an hour this potassium level gradually falls while the breathing gradually increases. Meanwhile the acidity of the blood increases to a pH of 6.78. The blood sugar and the lactic acid concentrations are both elevated. It is surprising that life can continue for several hours when the acidity is so abnormal. When CO_2 is removed there is another small rise in potassium, presumably due to changes in membrane equilibrium between the inside and outside of the cells. The potassium liberated by CO_2 probably comes from the liver and is absent in an eviscerated animal. Since the pattern of the breathing in an eviscerated animal is the same as in the intact animal the depression of breathing which occurs cannot be ascribed to the potassium.

In the experiments of Paul Bert with closed vessels the birds died not directly because the inspired air had become lethal but because with this particular inspired air the sparrow was no longer able to control the composition of the alveolar air within non-lethal limits by increasing the respiration. It is the alveolar air which is most important physiologically because it is this air which comes into equilibrium with the blood. I should like therefore to direct your attention now to various ways in which the alveolar point can be made to move on the oxygen-carbon dioxide diagram.

The first case is that of holding the breath which has been well worked out by my colleagues, Drs. Kann and Otis (1947). In a general way we may regard this experiment as similar to that of survival in a closed vessel with the difference that the vessel in this case is reduced to the size of the lung. This situation is illustrated in the next chart (fig. 4) plotted on the same coordinates as before. The alveolar air line represents the starting point at which breath holding begins at various altitudes. When the breath is held the composition of this alveolar air increases in CO_2 and decreases in oxygen along one of the paths indicated until the breaking point line is reached. At this point the stimulus to the breathing, as defined by the equation of Gray (1946) (shown on the chart) is enough to cause a rate of ventilation about eight times normal. This very useful empirical equation expresses the breathing stimulus as a function of CO_2 excess and oxygen lack. It was shown by Dr. Otis that this theoretical equation coincides roughly with the breaking point curve.

Three different breath holding pathways have been indicated on the chart. In pure oxygen at the right the breath can be held for an average of 153 seconds and the pathways must always lie on an R.Q. diagonal of slope equal to 1.0 if the total pressure remains constant, even though the actual CO_2 output is much less than the O_2 intake. In air at ground level in the middle of the chart the breath holding pathway indicates a large loss of oxygen for very little increment in carbon dioxide, the average R.Q. being only 0.1 and the average time 43 seconds. The low R.Q. is due

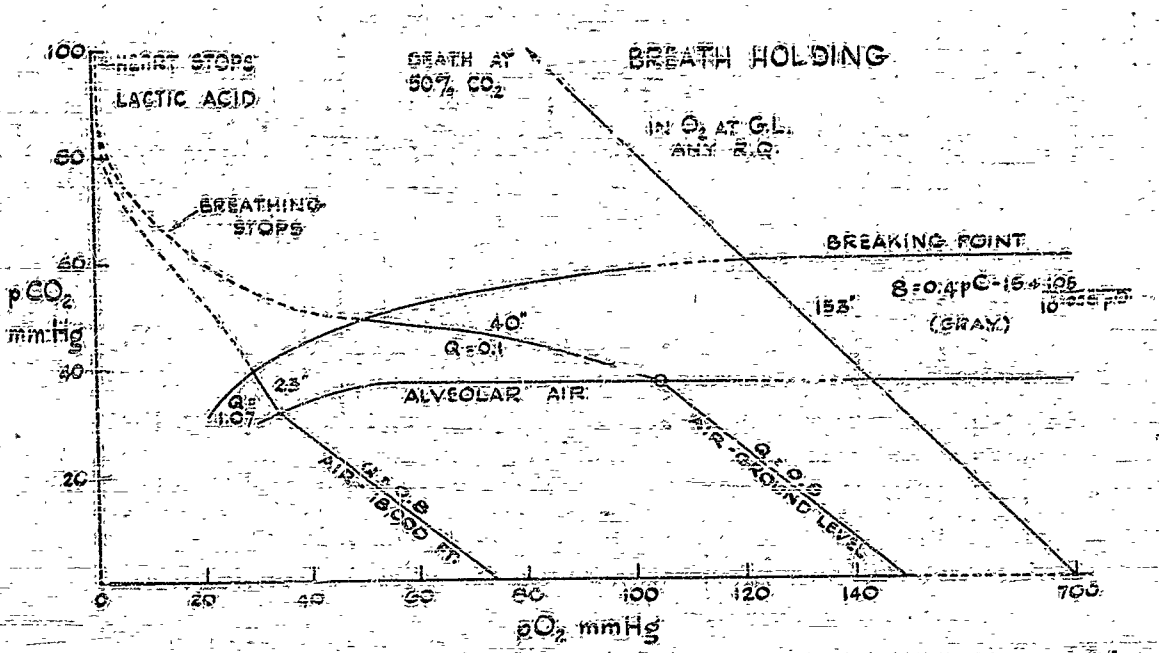

FIG. 4. Breath holding in pure O_2 at ground level (right), in air at ground level (middle) and at 18,000 feet simulated altitude breathing air (left). Ordinates and abscissae represent the pressures of CO_2 and O_2 respectively in the alveolar air in the lungs. Breath holding begins in each case at the alveolar air line and terminates at the breaking point line.

to the alkaline reserve of the body which combines with the carbonic acid when the concentration of CO_2 rises in the lungs. Experiments have shown that 1 liter of the body holds about as much carbon dioxide for 1 mm increase of pressure as 2.5 liters of gas volume in the lungs.[3] A 70 Kg man therefore can dispose of CO_2 in his body as well as if he were rebreathing 175 liters of air. Actually only about one-sixth of this equivalent volume is available during a breath holding experiment (with air at ground level) because the circulation does not have time to carry the CO_2 to all parts of the body.

The third breath holding pathway indicated is that at an altitude of 18,000 feet where the breath holding time is 23 seconds or less and most subjects come near fainting when the breaking point is reached. In this drastic experiment the R.Q. is high instead of low and the pathway on this chart is very steep. This is because the oxygen tension in the lung is so low that it promptly approaches the level of the venous blood so that no more O_2 can be taken up although the CO_2 is given off at the same rate as before. The CO_2 concentration at the breaking point is less than before because the stimulus due to low oxygen is greater and the sum of the two must add up, according to Gray's equation, to a constant value of about 8.

After the breaking point is reached the dotted lines show the probable further course which the alveolar air would follow if intake of air were prevented as in drowning or strangulation. These curves are based upon data (unpublished) obtained in my laboratory by Miss Florence Herber in experiments on anesthetized dogs. A few minutes after obstruction of the airway the breathing stops. Thereafter there is a continued rise in CO_2 tension as the oxygen falls to zero and the heart stops. Most of this terminal CO_2 must come from bicarbonate from which it is liberated by the lactic acid which forms in the muscles in considerable amounts and leaks into the blood. The CO_2 actually present in the muscles at death is 3 ml. per 100 gms. below normal in spite of the high CO_2 tension.

The terminal events when breathing pure oxygen at ground level as shown at the right in figure 4 are of special interest and of some practical importance. Consciousness is lost soon after the breaking point line is passed (if inhalation is prevented) and breathing movements may stop. In this case

[3] This figure is not exact and will be considerably less than this for high pressures of CO_2.

however the animal does not necessarily die so long [illegible] oxygen is used in the lungs more oxygen enters through the trachea and keeps the blood adequately oxygenated. CO_2 does continue to form but so much of it is retained within the body by the alkaline reserves that the CO_2 tension does not exceed 50 per cent of an atmosphere after 45 minutes. At this time the body of a man would contain an extra 14 liters of carbon dioxide, most of it in solution. This interesting experiment of Roth, Whitehead, and Draper (1947) shows that CO_2 itself is not lethal at the 10 per cent level but when breathing stops in air the oxygen in the lungs is soon exhausted and the man dies of anoxia. The exact point where apnoea begins is not known. A concentration of about 50 per cent CO_2 is lethal after a suitable period even though the oxygen supply is still sufficient.

Previous illustrations have shown two different kinds of R.Q. diagonals. In the experiments of Paul Bert the diagonals represent the progressive changes in the composition of the air of the closed vessel in which the animal was breathing. With an R.Q. of 0.6 the CO_2 goes up 6 mm when the O_2 goes down 10 mm (broken lines, figure 5).

The other kinds of R.Q. diagonal represents the composition of the *alveolar air* as a function of different rates of ventilation. Breathing more rapidly the alveolar point moves down the diagonal toward the inspired air point which corresponds to an infinite rate of ventilation. In these diagonals (solid lines, fig. 5), for an R.Q. of 0.6, the O_2 goes down only about 9 mm (instead of 10) when the CO_2 goes up 6 mm. The correct R.Q. lines can be plotted from the alveolar air equation shown in the slide. The reason for this difference is to be found in the volume change which occurs in the limited space of the lungs. When oxygen is consumed in excess of the CO_2 given out the volume of the gases in the lungs diminish and air comes in to fill the space. Thus, if the chest expands 1 liter, more than 1 liter of air comes in and in general more gas is inhaled than is exhaled. This extra inflow of air brings with it some fresh oxygen so that the resulting oxygen tension is a little greater than it otherwise would be. One of the advantages of this diagram is that it automatically takes care of complicated volume changes of this sort and the resulting dilutions. In Bert's experiments with closed vessels no fresh air could enter and the overall pressure must have fallen steadily. When the R.Q. is 1.0 both sets of diagonals are identical because there is no volume change. Likewise at any constant pressure or altitude where pure oxygen is inhaled the composition of the gases in the alveolar air must change

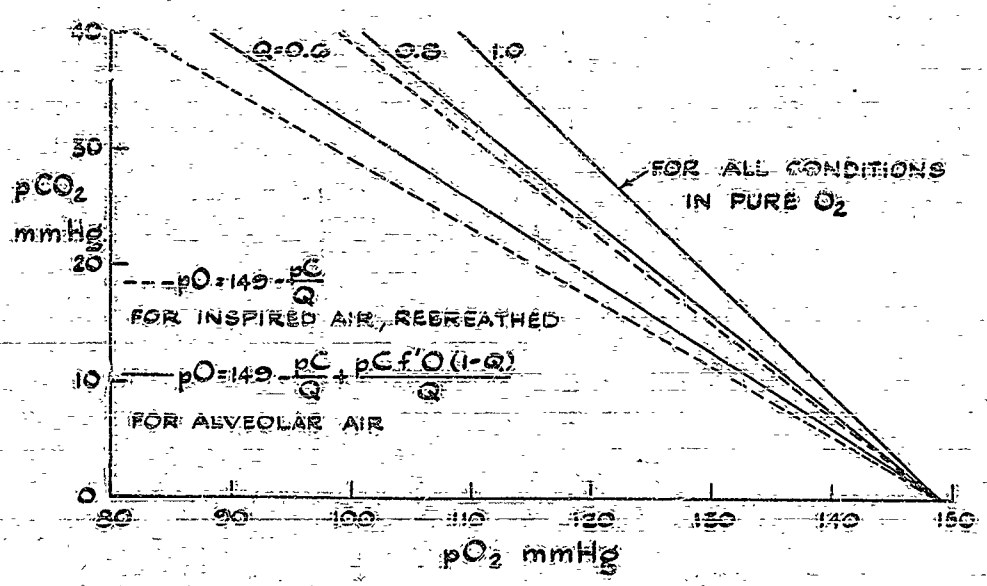

FIG. 5. The R.Q. diagonals for the inspired air in a closed vessel (broken) and for the alveolar air (solid) as indicated by the equations. The difference between two diagonals of the same CO_2/O_2 ratio (Q) is due to the volume change in the lungs and its magnitude depends upon the fraction of nitrogen in the inspired air.

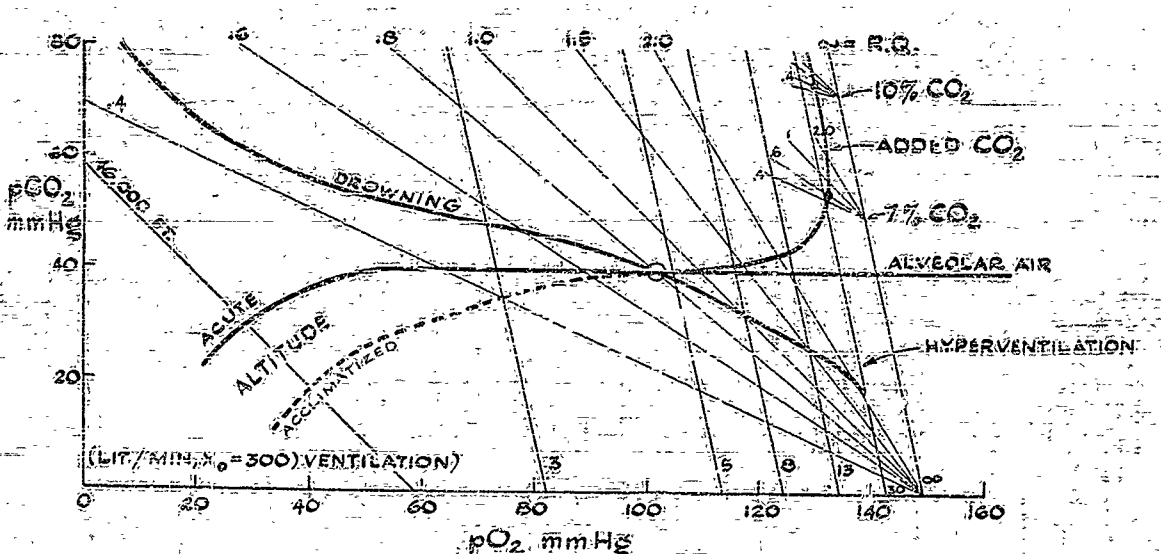

FIG. 6. The O_2-CO_2 diagram for ground level breathing air on the right and for 46,000 feet breathing pure O_2 in the left showing how all the R.Q. diagonals and isoventilation lines become reduced, in pure O_2, to a single 45 degree diagonal. The heavy lines represent movements of the alveolar point (represented by a circle) under different conditions.

along the diagonal marked R.Q. = 1 because, under such conditions, the sum of the pressures of these two gases must be equal to the dry gas pressure (B-47); a decrease in CO_2 of 10 mm must always be accompanied by an increase in O_2 of 10 mm or vice versa. Note that the alveolar air equation given in figure 5 reduces to $pO = 149 - pC$ when fO (the fraction of O_2 in the inspired air) = 1.0. This is the equation for the R.Q. = 1.0 line.

The next chart (fig. 6) illustrates further some important features of the oxygen-dioxide diagram. Ordinates and abscissae represent as before the concentrations or pressures of these two gases in the alveolar air. At 40 mm of CO_2 and 100 mm of O_2 is a point marked by a circle which represents the normal alveolar air at ground level breathing air. This is located on the alveolar air line which shows how the CO_2 concentration of the alveolar air changes as the oxygen content of the inspired air diminishes, as it does with altitude, for example. As illustrated in previous charts the alveolar point lies on a diagonal which represents the normal ratio (R.Q. = 0.8) of CO_2 formed in metabolism to the oxygen used up. For every R.Q. there is a diagonal of a different slope all radiating from the point which represents the composition of the inspired or the ambient air. This whole family of radiating R.Q. lines must be thought of as shifting about on the diagram as the point of origin or the inspired air point shifts. If therefore one goes to high altitudes and the pO_2 diminishes the R.Q. diagonals are shifted along the axis of abscissae to the left. If the CO_2 concentration of the inspired air increases then the diagonals are moved upwards correspondingly. Such a set of diagonals forms a background grid against which the movements of the alveolar point can be read and interpreted.

Another part of this same grid is formed by the isoventilation lines. Such lines are drawn for 3, 5, 8, 13, 30, and infinite liters of air breathed per minute. All these lines are parallel to one another and all are to be shifted to the left along with the R.Q. diagonals in proportion to a decrease in the oxygen content of the inspired air. If the rate of ventilation and the R.Q. are known then the alveolar point must be represented by the intersection of the appropriate R.Q. diagonal and isoventilation line and the corresponding pCO_2 and pO_2 values can then be read off. On this chart it can be seen that the ventilation rate is a little less than 5 liters per minute. All the isoventilation lines are calculated for a given rate of oxygen consumption (300 cc per min.). They all have a slight negative slope which is equal to the fraction of oxygen in the inspired air. The mathematical expression which defines the isoventilation

lines and the R.Q. diagonals are rather complicated and have been described in detail elsewhere (Fenn *et al.*, 1946). Isoventilation lines may also be calculated on the assumption that the rate of CO_2 output is constant and these are merely horizontal lines across the chart. All these isoventilation lines refer to the air which actually gets into the alveoli and excludes therefore that fraction of each breath which fills the dead space (nasopharynx and trachea, etc.) where no gas exchange occurs.

The heavy black lines in the chart show four "alveolar pathways" along which the alveolar point can move under different conditions. In the lower right hand corner is such a pathway resulting from hyperventilation. If the subject merely increases his breathing rate voluntarily from 5 to 30 liters per minute his alveolar point must move from the 5 to the 30 liter isoventilation line. If the R.Q. remains at 0.8 the alveolar point would be at the intersection of this isoventilation line with the R.Q. = 0.8 diagonal. At that point however the pCO_2 is so low that CO_2 escapes from the stores in the body in excessive amounts so that the R.Q. increases temporarily to 2.0 as indicated in the diagram. In the course of half an hour, if the ventilation rate is maintained, it then gradually falls to the 0.8 line as the excess CO_2 is blown off.

It is interesting to find that this hyperventilation pathway seems to be continuous with the breath holding or drowning pathway already described. In the former the concentration of CO_2 in the alveoli is prevented from falling too far by release of CO_2 from the CO_2 stores of the body and in the latter, extra CO_2 is stored by the body to prevent the alveolar CO_2 concentration from rising too high. It should also be noted that in the process of hyperventilation the alveolar point moves to higher oxygen tensions and this increase in oxygen tension is further favored by the increase in the R.Q. This explains the improvement which the aviator experiences when he instinctively hyperventilates at high altitudes in response to the lowered concentration of oxygen in his lungs. The improvement is greater and more noticeable when air is breathed than with pure oxygen because of this "fanning out" of the R.Q. lines.

In the upper right corner of the diagram is shown the curve which represents the alveolar points which would result if the percentage of carbon dioxide in the inspired air were gradually increased, as by the escape of CO_2 from a high pressure tank into the room. In this case the point representing the gas tensions of the inspired air rises along the curve marked R.Q. = infinity. The oxygen tension gradually falls along this line because the oxygen is diluted by the incoming CO_2. For each successive inspired air point along the R.Q. = ∞ line there could be drawn a set of diagonals similar to those of the chart. Two sets of such diagonals are drawn at the points where the inspired CO_2 was 7 and 10 per cent of an atmosphere and the corresponding alveolar points are indicated on the 0.6 and 0.4 diagonals respectively.[4] At 10 per cent CO_2 the breathing rate has increased to 50 liters per minute and the alveolar point is very close to the inspired air point.

In this experiment it is important to note that the alveolar oxygen tension is increased as the CO_2 increases because of the greater rate of ventilation. For this reason the intake of CO_2 at high altitudes is of some benefit (although a similar intake of extra O_2 is better). If however CO_2 is added to pure O_2 for inhalation at altitude, the CO_2 tension and the ventilation increase exactly as indicated in the chart for air but the oxygen tension decreases *pari passu* with the increase in CO_2 because in this case the sum of pO_2 and pCO_2 must always be equal. When CO_2 increases, O_2 must therefore decrease an equal amount. Attempts to demonstrate a benefit from adding CO_2 at altitude under such conditions (absence of nitrogen in the gas inspired) must eventually prove abortive.

The chart which I have described with its background grid of R.Q. diagonals and isoventilation lines is particularly useful when dealing with problems involving the inhalation of air or nitrogen-containing mixtures for the presence of nitrogen introduces interesting complications. The situation is much simpler when pure oxygen is breathed as already indicated in figure 5. As the fraction of oxygen in the inspired air increases the R.Q. diagonals progressively close up like a fan until in pure oxygen they coincide with the R.Q. = 1.0 diagonal. Likewise the isoventilation lines gradually pivot around their points of intersection with the R.Q. = 1.0 line until they also coincide with it. This applies only to the isoventilation lines calculated on the assumption that the rate of oxygen consumption re-

[4] These points and other points on this curve were calculated from an equation of Gray (1946).

mains constant. This is rational because when pure oxygen is inhaled the rate of oxygen consumption can have no effect upon the composition of the alveolar air; for every molecule of oxygen taken up in the lungs another molecule of oxygen will enter through the trachea. When the chest expands 1 liter more than 1 liter of oxygen will enter the lungs if the R.Q. is less than 1.0.[5] The isoventilation lines calculated for a constant rate of CO_2 output are not affected by changes in the oxygen content of the inspired air. When breathing pure oxygen, therefore, it is only the rate of ventilation and the rate of CO_2 output which determine the composition of the alveolar air.

These considerations show that the status of an aviator at high altitudes breathing pure oxygen can be represented as shown on the left of the chart in figure 6 by a single diagonal. The alveolar point must lie somewhere on this diagonal. For the particular altitude of 46,000 feet selected, the diagonal intercepts the axes at 59 mm this being the total pressure available (B-47 or barometric minus water vapor) for partition between CO_2 and O_2. If the ventilation rate remained at 5 liters per minute the alveolar pCO_2 would have been 40, as at sea level, and the alveolar pO_2 only 19 mm. If the ventilation rate were doubled, the alveolar pCO_2 would have been half as great or 20 mm and the alveolar O_2 would then be 39 mm. The problem of the respiration then is to breathe at such a rate that this pressure (B-47) is divided most advantageously between oxygen and carbon dioxide or so that the composition of the alveolar is as near as possible to the "normal range" indicated in figure 1. Our experiments have lead us to believe that on the average at high altitudes we instinctively breathe nearly but perhaps not quite fast enough for optimal performance.

This applies to an acute exposure to high altitudes like that obtained in an airplane. If one remains indefinitely at that altitude the rate of breathing continues to increase for a week or more as the sensitivity to carbon dioxide increases. This is shown by the dotted alveolar line for acclimatized men which was kindly supplied to me by my colleague, Dr. Rahn. This was drawn partly from his own data (obtained with Dr. Otis in Wyoming) and partly from the data of other mountain expeditions.

[5] This somewhat paradoxical statement is true if one considers the decrease in volume which occurs in the lungs before this liter is exhaled.

Another feature of acclimatization is the increased number of red blood corpuscles in the blood. In our laboratory Mr. R. T. Clark has recently shown that mice can tolerate exposures to high altitudes much better if they have been kept previously for a week or more in an atmosphere containing small amounts of carbon monoxide for this also increases the number of corpuscles. Another fact of extraordinary interest which seems to be appearing in his experiments is the fact that the CO in the closed vessel in which the mice are kept tends to disappear at an easily measurable rate which cannot be accounted for by combination with hemoglobin. This does not happen after the mice are removed. This experiment seems to confirm an observation which I made years ago in experiments with excised tissues which showed that CO can be burned to CO_2 by the oxidative enzymes existing in muscle.

The few examples which I have time to put before you could be multiplied almost indefinitely. In our laboratory for example we have devised an automatic device which continuously draws off the last of each breath and analyzes it electrically for both oxygen and carbon dioxide. In this way it is not difficult to obtain continuous records of the alveolar pathways in normal and pathological subjects when engaging in a great variety of respiratory experiments. These records are proving of great interest to the clinicians as well as to the physiologist. Eventually we hope to develop this into a simple instrument for bedside diagnosis. The complete interpretation of such experiments would require a rather complicated mathematical analysis but this is very much facilitated by the use of the graphical methods which I have tried to describe for you.

Man has been breathing just as he does today since the dawn of science. During that long time he has developed innumerable intricate machines the behavior of which has been analyzed mathematically in complete detail. A small fraction of this attention devoted to the understanding of the respiratory machinery would have elucidated that mechanism with equal perfection. It was not, however, until the exigencies of the recent war turned the attention of many minds to respiratory problems of high altitude flying that anyone clearly perceived the need for a strict mathematical treatment of the dynamics of pulmonary ventilation. Now through the independent efforts of several different laboratories we have at least an alveolar air equation and a ventilation equation

which define the steady state and these are nicely represented on our chart by convenient straight lines. Much more remains to be done in defining unsteady states and correlating respiratory and circulatory dynamics but it is hoped that what has already been accomplished represents in a small way a somewhat belated "promotion of useful knowledge."

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ALVEOLAR AIR DURING SIMULATED FLIGHTS TO HIGH ALTITUDES[1]

HERMANN RAHN AND ARTHUR B. OTIS

Heretofore, practically all extensive measurements of alveolar gas composition have been made on samples intermittently obtained from forcible expirations. Such methods require a certain amount of co-operation on the part of both subject and operator, and are bound to interfere with the normal breathing pattern. The sampling and analyzing device described by Rahn, Mohney, Otis, and Fenn (1946) makes possible the continuous sampling and minute to minute recording of alveolar air of a subject quietly breathing from a face mask. The purpose of the present investigation was to obtain by this method extensive data concerning the respiratory behavior of several thoroughly trained subjects[2] breathing under normal resting conditions and under a variety of experimental conditions, particularly during acute exposure to the simulated altitudes of 12, 16, 18, 20, and 22 thousand feet.

Outline of Flights. Series I–V. All experiments were begun at 9 a.m. or 2 p.m. The subject was seated in the high altitude chamber during all measurements and breathed air through a face mask from a Pioneer demand valve. After a twenty minute period at ground level (540 ft., elevation above sea level), during which control measurements were made, ascent to the desired altitude occurred at a rate of 4500 feet per minute. An observer breathing oxygen accompanied the subject. Measurements were resumed as soon as the desired altitude was reached. Experiments were one hour in length at the 12, 16, and 18 thousand foot altitudes, 45 minutes at 20,000 feet and 30 minutes at 22,000 feet. Each subject was exposed to each altitude from lowest to highest in turn with at least a one day interval between successive exposures. The same eight subjects participated in all these experiments. Series III A was identical with series III.

Series VI and VII. In addition to the "normal" flights (series I to V) each of the eight subjects also participated in similar one-hour flights to 12,000 and 18,000 feet which were preceded by the ingestion of 100 grams of glucose in 200 cc. of water just before the ascent.

Series VIII. CO_2 inhalation at 16,000 feet: in this series four subjects breathed 6.0 per cent CO_2 in air for a 15 minute period. The experimental

[1] Work done under contract recommended by Committee on Medical Research between the Office of Scientific Research and Development and the University of Rochester.

[2] We wish to acknowledge the splendid co-operation of the following members of Civilian Public Service Unit No. 115-R who served as efficient subjects, observers, and recorders during the several months of tedious routine required to complete these measurements: R. Dick, I. Eller, J. Heil, T. Horvath, R. Long, B. Miller, H. Mitchell, R. Ortmayer, G. Spicer, R. Stanley, M. Whitaker.

period was preceded by a 10-minute control period and followed by a 10-minute recovery period, both at 10,000 feet. No performance tests were administered during these experiments.

Series IX and X. Muscular work at ground-level and 16,000 feet. For the muscular work, the sitting subject pushed his feet alternately against pedals constructed from flat pieces of spring steel at a rate of 30 times a minute for each foot. The mechanical work required for this task was calculated to be 49.4 kilogram-meters per minute. The period of actual work was 10 minutes in length. It was preceded by a control period and followed by a recovery period of the same duration.

METHODS. *Alveolar gas composition* was read and recorded each minute by use of the continuous method referred to above. In addition, an end-expiratory Haldane-Priestley sample was obtained every ten minutes and subsequently analyzed by the Haldane method or by the same meters used for the continuous method. The discrepancy between the conventional and the continuous methods was thus obtained.

Frequency of breathing was recorded outside the chamber on a paper tape which moved at a known constant rate. The slight negative pressure developed in the mask during each inspiration was made to close a relay circuit by means of a switch constructed from a sensitive aneroid barometer. Closure of the circuit activated an electromagnet to which was attached the recording pen, which thus made a deflection during each inspiration.

Ventilation volume was recorded on the same tape by another electro-magnetically operated pen. The subject expired through a gas meter so fitted with electrical contacts that its rotating arm briefly closed the pen circuit once for each 500 cc. of gas passing through the meter. The temperature was read from a thermometer inserted into the outlet of the meter.

Percentage saturation of the arterial blood was read and recorded each minute by means of the Millikan oximeter using the single scale circuit with automatic adjustment for ear thickness (Millikan, 1942).

Heart rates were recorded for one minute out of each ten by means of an electrocardiotachometer.

Performance was measured every ten minutes by the hand steadiness test previously described (Rahn, Otis et al.).

RESULTS. *Normal runs (series I through V) and glucose runs (series VI and VII).* The data obtained are summarized in tables 1–3. Respiratory data are averages of the minute to minute readings of each five-minute period indicated. Each value, therefore, is based on five measurements on each subject or a total of 40 separate readings, except in series III A, in which only six subjects participated and in series V in which one subject lost consciousness after ten minutes at altitude. Heart rates and steadiness test scores are indicated at ten minute intervals as explained in the legend accompanying the tables.

Carbon dioxide inhalation experiments (series VIII) and exercise runs (series IX and X) are summarized in tables 3 and 4, respectively, which are similar to the previous tables except that the respiratory data are averaged for 2-minutes in-

TABLE 1

	TIME—MINUTES															
	5	10	15	20	5	10	15	20	25	30	35	40	45	50	55	60
	Ground Level, B = 746				12,000 Ft. B = 483, Series I											
1. Alveolar pO_2	102.2	100.8	101.5	101.0	54.5	52.1	51.2	51.0	50.0	50.4	49.5	51.4	51.2	50.9	49.4	50.7
2. Alveolar pCO_2	37.9	37.2	36.8	37.6	35.1	35.4	35.1	35.1	35.2	34.9	35.3	34.5	34.3	34.3	35.1	34.6
3. Alveolar R.Q.	0.82	0.80	0.81	0.81	0.95	0.89	0.86	0.85	0.83	0.85	0.83	0.83	0.83	0.83	0.81	0.82
4. Ventilation l./min.	8.80	9.10	9.02	8.85	10.60	9.45	9.82	9.48	9.42	9.50	9.55	9.36	9.72	9.61	9.80	9.77
5. Breaths/min.	13	14	14	13	16	14	14	13	14	14	14	14	14	14	15	14
6. % HbO_2 (Calc.)					89	88	87	87	86	87	86	88	87	87	86	87
7. % HbO_2 (Oximeter)				98	89	87	85	86	85	85	84	85	85	85	85	85
8. Ml. O_2/min. (Calc.)	314	334	327	324	312	302	327	319	321	313	326	325	326	317	336	331
9. Heart Rate % Normal			*(82)	100		113		115		113		106		104		99
10. Stead. Test % Normal			*(386)	100		129		157		104		139		138		113
	Ground Level, B = 751				16,000 Ft. B = 412, Series II											
1. Alveolar pO_2	107.1	107.9	107.0	106.1	46.1	45.6	44.4	44.8	46.1	45.4	44.4	43.2	44.2	44.4	43.5	44.2
2. Alveolar pCO_2	35.1	34.6	34.9	34.9	32.4	30.8	30.8	30.0	28.5	28.6	28.9	29.4	28.8	28.2	27.9	28.0
3. Alveolar R.Q.	0.86	0.87	0.83	0.83	1.11	1.03	0.99	0.96	0.98	0.95	0.91	0.97	0.89	0.87	0.82	0.86
4. Ventilation l./min.	8.69	8.69	8.61	8.25	9.50	9.32	8.98	9.14	9.40	9.72	9.36	8.79	9.76	9.39	8.90	10.50
5. Breaths/min.	11	12	12	13	12	12	11	11	11	13	12	12	12	12	13	11
6. % HbO_2 (Calc.)					85	85	84	84	85	85	84	83	82	85	84	84
7. % HbO_2 (Oximeter)					82	80	78	79	79	79	80	78	80	81	79	82
8. Ml. O_2/min. (Calc.)	301	281	297	273	233	225	244	244	236	248	248	250	270	254	258	306
9. Heart Rate % Normal			*(81)	100		111		110		103		103		101		105
10. Stead. Test % Normal			*(326)	100		91		154		265		210		180		196

	Ground Level, B = 751				18,000 ft., B = 379, Series II.										
1. Alveolar pO_2	108.2	105.3	105.5	107.1	44.1	43.1	41.8	41.3	41.5	40.1	41.1	40.6	40.2	39.8	40.3	41.1
2. Alveolar pCO_2	34.6	34.9	34.8	35.0	28.8	28.4	28.0	27.3	26.6	27.0	26.7	26.2	25.7	26.2	25.4	25.1
3. Alveolar R.Q.	0.88	0.82	0.82	0.86	1.23	1.15	1.06	1.02	0.99	0.94	0.93	0.93	0.90	0.88	0.88	0.90
4. Ventilation l./min.	8.55	8.45	8.49	8.42	11.38	10.90	11.02	11.24	11.24	11.06	11.10	11.73	11.43	10.66	10.63	10.83
5. Breaths/min.	12	11	12	12	11	11	11	12	12	11	11	11	12	12	12	11
6. % HbO_2 (Calc.)					84	84	82	82	82	81	81	82	81	81	82	83
7. % HbO_2 (Oximeter)					80	79	77	78	75	75	76	76	77	77	76	78
8. Ml. O_2/min. (Calc.)	275	304	294	279	246	246	266	271	271	295	292	307	296	282	272	275
9. Heart Rate % Normal			*(82)	100		107		109		108		111		108		104
10. Stead. Test % Normal			*(301)	100		676		372		405		442		458		392

Each column contains average values on all subjects during the indicated period of time. The meaning of the rows is as follows:

1. The alveolar oxygen tension in millimeters of mercury.
2. The alveolar carbon dioxide tension in millimeters of mercury.
3. The alveolar respiratory quotient as calculated by equation (6) from Fenn, Rahn, and Otis, 1946.
4. The ventilation rate in liters per minute calculated at B.T.P.S. (body temperature, ambient pressure, saturated).
5. The frequency of breathing per minute.
6. The percentage saturation of the arterial blood as estimated from the alveolar pCO_2 and pO_2 with the nomogram of L. J. Henderson (1928).
7. The percentage saturation of arterial blood as indicated by the Millikan oximeter.
8. The oxygen consumption in milliliters per minute S.T.P. calculated from the relationship

$$X_o = \frac{V_a \times pC}{0.864 \times Q}$$

Where V_a = alveolar ventilation in liters per minute (B.T.P.S.)
pC = alveolar pCO_2 in mm. Hg
Q = alveolar respiratory quotient

$$0.864 = \frac{310}{273} \times \frac{760}{1000}$$

A constant dead space of 210 cc. was assumed in computing V_a from the total ventilation (150 cc. personal dead space plus 60 cc. apparatus dead space).

9. The heart rate as per cent of the resting heart rate at ground level. These values are averages based on several measurements during each indicated 10-minute period. The average value for the control rate in beats per minute is the figure in parentheses indicated by an asterisk.

10. Steadiness test score as per cent of the average value at ground level. The actual value of the ground level score expressed as time of contact in 1/240 second out of a 30-second test period is the value in parentheses indicated by an asterisk. The steadiness test was administered every 10 minutes and so appears in alternate 5-minute periods.

Each figure in series I–VII represents an average of (8 × 5) 40 readings. The R.Q. is the average taken from the original data and may differ slightly when computed from average oxygen and carbon dioxide values in these tables, due to dropping of decimals and rounding off.

TABLE 2

	TIME—MINUTES															
	5	10	15	20	5	10	15	20	25	30	35	40	45	50	55	60
	Ground Level, B = 746				18,000 Ft. B = 379, Series III-A											
1. Alveolar pO_2	100.8	103.1	102.3	104.4	43.4	42.3	40.8	39.8	40.5	40.5	39.7	38.5	39.6	38.9	38.6	36.6
2. Alveolar pCO_2	37.4	36.4	36.5	36.3	29.3	27.6	27.7	28.5	26.8	26.1	27.1	28.3	27.1	26.6	27.0	28.3
3. Alveolar R.Q.	0.79	0.82	0.81	0.84	1.22	1.13	1.00	0.99	0.94	0.94	0.95	1.02	0.96	0.89	0.87	0.87
4. Ventilation l./min.	8.99	9.26	9.24	8.93	13.51	13.11	12.96	12.03	12.33	11.02	12.06	11.35	12.18	10.68	11.06	10.38
5. Breaths/min.	15	15	14	15	12	12	14	14	14	13	15	15	15	13	14	14
6. % HbO_2 (Calc.)					82	83	81	80	82	82	81	80	80	80	79	77
7. % HbO_2 (Oximeter)					79	77	75	73	73	75	74	71	73	72	73	70
8. Ml. O_2/min. (Calc.)	318	312	330	287	306	302	334	304	312	267	272	237	303	276	293	232
9. Heart Rate % Normal			*(88)	100		112		111		113		104		99		107
	Ground Level, B = 745				20,000 Ft. B = 349, Series IV											
1. Alveolar pO_2	104.1	104.2	100.7	104.8	39.8	37.6	36.8	36.7	36.4	36.4	36.8	37.9	37.0			
2. Alveolar pCO_2	36.5	35.1	37.0	35.5	27.1	26.6	26.3	24.4	25.6	24.4	24.5	25.4	23.2			
3. Alveolar R.Q.	0.85	0.85	0.79	0.85	1.21	1.03	0.97	0.94	0.93	0.94	0.89	0.89	0.84			
4. Ventilation l./min.	8.30	8.71	8.12	8.40	13.77	12.36	12.66	11.76	12.23	12.46	12.60	13.44	12.56			
5. Breaths/min.	13	12	11	11	11	11	11	11	12	12	12	13	13			
6. % HbO_2 (Calc.)					81	79	78	76	78	80	79	80	79			
7. % HbO_2 (Oximeter)					78	74	74	73	72	74	75	77	76			
8. Ml. O_2/min. (Calc.)	278	297	315	296	298	301	325	284	310	299	321	326	315			
9. Heart Rate % Normal			*(84)	100		124		112		117		107				
10. Stead. Test % Normal			*(362)	100		365		651		923		775				
	Ground Level, B = 747				22,000 Ft. B = 321, Series V											
1. Alveolar pO_2	105.0	103.9	102.9	103.3	36.1	34.0	33.6	32.7	31.8	32.0						
2. Alveolar pCO_2	34.7	35.2	35.5	35.3	24.4	25.1	23.8	24.6	24.1	23.5						
3. Alveolar R.Q.	0.83	0.81	0.82	0.81	1.26	1.11	1.05	1.01	0.95	0.95						
4. Ventilation l./min.	8.72	8.18	8.57	8.64	16.79	14.61	15.82	15.21	14.15	15.31						
5. Breaths/min.	10	11	11	11	14	12	14	14	14	15						
6. % HbO_2 (Calc.)					78	75	75	73	72	72						
7. % HbO_2 (Oximeter)					73	68	69	66	63	64						
8. Ml. O_2/min. (Calc.)	321	296	315	320	311	317	338	347	330	359						
9. Heart Rate % Normal			*(88)	100		121		126		124						
10. Stead. Test % Normal			*(365)	100		354		1217		1702						

TABLE 3

	TIME—MINUTES																							
	5	10	15	20	5	10	15	20	25	30	35	40	45	50	55	60								
	Ground Level, B = 749				12,000 Ft. B = 483, Series VI—Glucose																			
1. Alveolar pO_2	101.6	101.5	103.8	102.9	54.4	52.8	52.6	52.6	52.1	52.7	51.7	52.1	53.2	57.8	54.5	62.7								
2. Alveolar pCO_2	37.9	38.5	36.5	37.4	34.6	35.2	34.9	34.5	34.7	34.8	34.9	34.4	34.8	38.0	34.5	34.2								
3. Alveolar R.Q.	0.83	0.85	0.84	0.83	0.95	0.91	0.90	0.89	0.89	0.87	0.87	0.87	0.90	0.88	0.93	0.83								
4. Ventilation l./min.	7.72	8.12	8.09	8.34	9.34	9.03	9.37	8.99	9.29	8.96	8.91	8.97	9.33	8.91	9.32	8.67								
5. Breaths/min.	12	13	12	12	12	12	13	12	13	12	13	12	12	12	12	11								
6. % HbO_2 (Calc.)					80	89	88	89	88	89	88	88	89	89	89	89								
7. % HbO_2 (Oximeter)					89	89	88	86	86	86	87	84	86	86	87	87								
8. Ml. O_2/min. (Calc.)	276	288	281	304	289	294	300	290	296	299	289	300	301	287	305	285								
9. Heart Rate % Normal			*(86)	100		110		109		104		107		109		102								
10. Stead. Test % Normal			*(251)	100		119		119		98		115		143		137								
	Ground Level, B = 749				18,000 Ft. B = 379, Series VII—Glucose																			
1. Alveolar pO_2	103.0	102.0	101.5	102.8	41.7	39.7	39.2	38.6	38.3	38.9	37.7	38.1	38.0	38.5	38.1	37.6								
2. Alveolar pCO_2	37.6	37.8	38.3	37.5	29.8	30.5	28.4	30.5	29.9	30.1	30.2	29.5	29.4	30.2	29.2	29.4								
3. Alveolar R.Q.	0.84	0.82	0.82	0.83	1.11	1.04	1.04	1.00	0.98	0.99	0.96	0.95	0.93	0.94	0.93	0.95								
4. Ventilation l./min.	8.40	7.66	8.39	8.02	12.45	11.23	12.13	11.13	11.10	11.00	11.26	11.26	11.53	11.00	11.60	11.32								
5. Breaths/min.	11	11	11	11	12	12	14	12	11	12	16	13	15	15	13	16								
6. % HbO_2 (Calc.)					82	80	79	79	79	79	77	78	76	78	78	79								
7. % HbO_2 (Oximeter)					82	81	79	78	78	79	78	77	78	78	79	79								
8. Ml. O_2/min. (Calc.)	315	287	329	298	310	296	293	304	311	299	286	308	305	291	320	284								
9. Heart Rate % Normal			*(85)	100		125		122		122		121		120		121								
10. Stead. Test % Normal			*(324)	100				386		615		522		373		389								

TABLE 3—*Concluded*

	TIME—MINUTES																	
	2	4	6	8	10	12	14	16	18	20	22	24	25	27	29	31	33	35
	Series VIII.—6% CO_2 at 16,000 Feet																	
	Normal					6% CO_2								Return to Normal				
1. Alveolar pO_2	49.0	47.8	47.2	47.9	46.4	46.1	47.4	47.7	48.1	48.9	49.3	49.2	49.4	47.9	46.4	46.2	45.4	45.9
2. Alveolar pCO_2	32.0	30.9	30.9	30.0	30.5	38.3	40.0	40.2	41.4	41.2	41.4	41.5	41.5	35.7	32.2	31.9	31.9	31.7
3. Alveolar R.Q.	1.22	1.13	1.11	1.09	1.05	0.89	0.72	0.77	0.82	0.82	0.86	0.85	0.85	1.39	1.12	1.13	1.07	1.08
4. Ventilation l./min.	13.87	12.36	12.73	13.87	12.14	12.79	13.80	15.16	15.10	15.45	15.09	15.96	15.37	14.95	12.56	12.07	12.10	11.83
5. Breaths/min.	11	12	11	10	10	11	12	14	12	13	14	14	13	13	12	11	11	10
6. Heart Rate					87								79					83
7. % HbO_2 (Calc.)	88	87	86	87	85	84	84	84	83	84	85	85	85	86	86	85	85	85
8. Oximeter	87	86	85	86	84	84	85	85	85	84	84	84	84	85	82	82	81	81

stead of for 5-minute periods. Grand averages for each 10-minute period are also shown in table 4.

DISCUSSION. 1. *Alveolar Gas Composition and Ventilation at Altitude.* The data presented for series I through V represent respiratory behavior typical of healthy, young, well trained male subjects during acute exposure to simulated altitudes. It should be emphasized that all subjects were thoroughly indoctrinated beforehand, and that they worked as a full-time laboratory team as subjects and technicians during the course of the experiments. They were, therefore, largely free of the apprehension that sometimes occurs in the case of individuals who are used only occasionally as subjects.

An important feature of the present data, made conveniently possible by the method of sampling, is that the time course of changes in alveolar gas composition is traced throughout the period of exposure to altitude. In this respect these data supplement the standard alveolar curves of Boothby (1944), which are based on values obtained at 10 and 15 minutes at altitude. Furthermore his subjects went successively to higher altitudes on the same run, thus partially adapting at each level. These time changes are strikingly reflected by the values for the alveolar respiratory quotient. Upon arrival at altitude the R.Q. is increased above normal owing to the hyperventilation resulting from the stimulus of anoxia. This hyperventilation is accomplished largely by increased tidal volume until 22,000 feet where the rate also increases. With time the CO_2 stores of the body are depleted and the R.Q. gradually drops back toward normal indicating the approach of a new steady state. Related to this changing R.Q. are the changes in alveolar gas tensions. The pO_2, relatively high at first, gradually drops with the R.Q. even though the pCO_2 may remain approximately constant or become considerably diminished. The percentage saturation of the arterial blood also tends to drop in parallel with the pO_2.

These significant facts are conveniently summarized graphically in figure 1 by use of the CO_2-O_2 diagram introduced by Fenn, Rahn and Otis (1946). Since the family of R.Q. lines have the same slopes but a different intercept at different altitudes, the various altitudes involved may be represented on a single set of R.Q. lines by use of a multiple scale of abscissae. This has been done for convenience in figure 1. In addition, lines of constant alveolar ventilation have been drawn for the values of 6, 8, 10, and 12 liters per minute on the assumption that the O_2 intake is constant. The locations of these lines were determined from equation 19 of our previous report (Fenn, Rahn and Otis, 1946). X_0 in this case, was taken as 300 cc. per minute, the average calculated oxygen consumption during the flights represented on the diagram. This seemed justifiable because no consistent effects of the altitudes on oxygen consumption can be observed in the data.

Several pertinent facts are emphasized by this mode of presentation. One may think of the immediate respiratory response to a given altitude as being represented by a jump from the ground level alveolar point on the diagram to the initial altitude point. During the first five minutes at any altitude the alveolar ventilation is greater than during the subsequent periods. This reflects the

TABLE 4

	TIME—MINUTES														
	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
Series IX.—Work at Ground Level															
	Resting					Work B = 746					Recovery				
1. Alveolar pO_2	101.3	101.5	101.7	102.2	100.1	94.5	96.9	97.6	98.7	98.5	102.8	101.9	102.4	102.0	102.8
2. Alveolar pCO_2	37.7	37.8	38.0	37.3	38.5	41.7	41.4	41.3	41.3	41.0	37.7	38.0	37.5	37.5	36.7
3. Alveolar R.Q.	0.83	0.82	0.86	0.85	0.83	0.79	0.83	0.83	0.86	0.84	0.87	0.86	0.85	0.84	0.84
4. Ventilation l./min.	9.12	8.72	8.63	8.79	9.06	12.18	12.83	13.99	14.85	13.94	10.81	8.85	8.89	8.81	8.76
5. Breaths/min.	12	12	12	12	12	15	14	15	15	16	13	13	13	13	13
6. Ml. O_2/min. (Calc.)	349	332	314	320	353	548	632	622	661	595	407	315	315	315	306
7. Heart Rate					84					92					87
Series X.—Work at 16,000 Feet															
	Resting					Work B = 412					Recovery				
1. Alveolar pO_2	46.6	44.6	44.2	43.4	43.0	41.0	40.6	40.3	39.6	39.8	41.6	41.3	41.6	41.0	40.8
2. Alveolar pCO_2	33.6	33.8	33.6	33.3	33.4	35.3	35.2	35.3	35.3	34.9	33.3	33.3	33.5	32.6	33.2
3. Alveolar R.Q.	1.19	1.12	1.08	1.04	1.02	1.02	1.00	0.97	0.97	0.97	0.93	0.95	0.96	0.92	0.94
4. Ventilation l./min.	11.07	11.46	11.09	11.09	11.38	16.01	17.65	17.63	17.65	17.58	13.10	10.98	10.11	9.99	10.25
5. Breaths/min.	12	12	12	12	11	14	15	15	15	17	12	13	11	12	11
6. % Hb O_2 (Calc.)	85	83	83	82	82	78	78	78	77	76	80	80	80	80	79
7. % Hb O_2 (Oximeter)	81	80	78	78	78	74	73	73	72	71	74	74	76	76	75
8. Ml. O_2/min. (Calc.)	280	313	320	319	344	526	589	607	609	594	426	348	316	307	325
9. Heart Rate					95					107					92

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Averages for Each Period

Series VIII.—6% CO_2

	Normal	6% CO_2	Normal
1. Alveolar pO_2	47.9	48.3	46.4
2. Alveolar pCO_2	30.9	40.4	32.7
3. Alveolar R.Q.	1.12	0.82	1.16
4. Ventilation l./min.	12.99	14.84	12.70
5. Breaths/min.	11	13	11
6. Heart Rate	87	79	83
7. % HbO_2 (Calc.)	87	84	85
8. Oximeter	85	94	82

Series IX.—Work at Ground Level

	Resting	Work	Recovery
1. Alveolar pO_2	101.4	97.2	102.4
2. Alveolar pCO_2	37.9	41.3	37.5
3. Alveolar R.Q.	0.84	0.83	0.85
4. Ventilation l./min.	8.86	13.76	9.22
5. Breaths/min.	12	15	13
6. Ml. O_2/min. (Calc.)	334	512	332
7. Heart Rate	84	92	87

Series X.—Work at 10,000 Feet

	Resting	Work	Recovery
1. Alveolar pO_2	44.4	49.2	41.3
2. Alveolar pCO_2	33.5	35.2	33.2
3. Alveolar R.Q.	1.09	0.99	0.95
4. Ventilation l./min.	11.22	17.50	10.89
5. Breaths/min.	12	15	12
6. % HbO_2 (Calc.)	83	78	80
7. % HbO_2 (Oximeter)	79	73	75
8. Ml. O_2/min. (Calc.)	306	535	304
9. Heart Rate	95	107	92

action of the initial anoxic stimulus which shortly is reduced in its net effectiveness because of the opposing inhibitory stimulus of acapnia. The pCO_2 tends to drop throughout the period of exposure to altitude, and as a consequence of this progressive acapnic state, the ventilation rate likewise gradually diminishes even

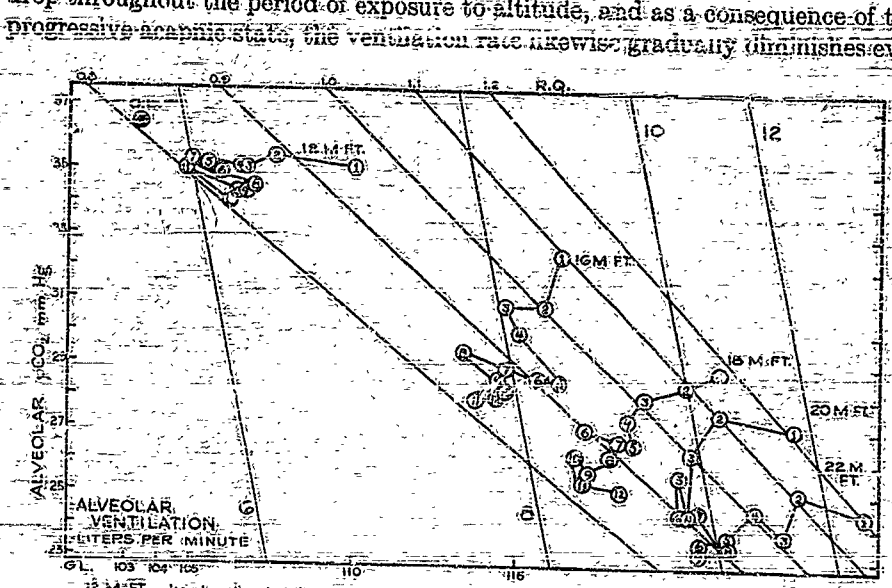

Fig. 1. The alveolar pathway during acute exposure to altitude.

Ordinates: Alveolar carbon dioxide tensions in millimeters of mercury.

Abscissae: Alveolar oxygen tensions in millimeters of mercury. Each of the multiple scales of abscissae applies to the family of points labelled with the corresponding altitude on the diagram.

Parallel diagonals: Isoventilation lines constructed by use of equation (19) from Fenn, Rahn and Otis, 1946.

Converging diagonals: Lines of constant R.Q. located by means of equation (9) from the same source.

The location of each member of the family of circles for a given altitude indicates the average composition of the alveolar air during a five-minute interval. The circles in each family are numbered consecutively, "1" indicating the first five minutes at altitude, "2", the second five minutes, etc. The solid circle indicates the average alveolar composition during the control periods at ground level, and hence is a sort of starting point from which changes may be followed as described in the text.

though the stimulus from anoxia is increasing. Comparing the different altitudes, one sees that the higher the altitude, the greater is the ventilation, the larger is the initial rise in the alveolar respiratory quotient, and the lower does the alveolar pCO_2 fall. The marked temporary gain in alveolar pO_2 by virtue of the initially high R.Q. is also readily apparent in this diagram. Lines indicating the

degree of oxygenation of the arterial blood could also be added but they would be different for different altitudes. By the end of the one hour exposure to altitude, the alveolar R.Q. has dropped nearly back to normal, indicating the approach to a new steady state. Although the 20,000 and 22,000 foot flights were not continued for this length of time, the trend of the points indicates that one hour would also suffice at these altitudes for attainment of an approximate steady state.

The alveolar pathway to this new steady state is not precisely linear, for the lines connecting the consecutive five-minute points form a zig-zag route which occasionally doubles back on itself. Some of these irregularities may be attributed to "hunting" on the part of the respiratory center for some minimum stimulus. Others may be due to extraneous sensory stimuli difficult to define or control. However devious the detailed path may be, there is no doubt as to the net direction. On teleological grounds this particular direction might be presumed to represent the points of optimum performance. Our evidence indicates, however, that in general the performance as measured by our tests is improved by ventilating somewhat faster than one actually does (Otis, Rahn, Epstein, and Fenn, 1946). Apparently the average subject tends to economize on respiratory effort somewhat to his own disadvantage. In exposures of greater duration the less well understood and more slowly acting processes of acclimatization must become of importance.

Only one of the eight subjects failed to complete the prescribed schedule of flights. It is of interest to note that this individual, who collapsed after ten minutes at 22,000 feet, consistently showed a smaller ventilation increase at altitude and consequently a higher alveolar pCO_2, and a lower oximeter reading than did the other subjects. Another subject, on the other hand, was somewhat inclined to nervous hyperventilation, but completed all flights without mishap.

The recovery at ground level following the flights was observed in a limited number of cases. The alveolar pathway upon recovery shows a reversal of the processes described above. Since the anoxic stimulus is no longer present, the acapnic inhibition of ventilation is free to exert itself until the CO_2 stores of the body are restocked. During this period of diminished ventilation, the alveolar R.Q. is lower than normal, and gradually rises to the resting value. The rate of return to normal pCO_2 values depends upon the previous anoxic hyperventilation at altitude. The higher and the longer the altitude exposure, the longer the recovery. The alveolar pathway is similar to that following hyperventilation as described by Rahn, Mohney et al., 1946. The R.Q. dips below 0.8 and slowly returns to normal with a consequent rise in pCO_2, pO_2 and ventilation rate as the CO_2 stores of the body are replenished. Thus acute exposure to altitude and recovery are represented on the CO_2-O_2 diagram by a closed circular or elliptical pathway bisected by the metabolic R.Q. line to which the body eventually returns both at altitude and during recovery from altitude. This is illustrated in figure 2 drawn from average values obtained on seven subjects after 30 minutes at 22,000 feet.

The value of the continuous sampling method in following the time course of

respiratory changes has been demonstrated above. As has been previously reported (Rahn, Otis, Mchney and Fenn, 1946) the continuous method gives values for the alveolar pCO_2 which are slightly lower and values for the alveolar pO_2 which are slightly higher than those given by the conventional Haldane-Priestley method. The additional data obtained in the present experiments bear this out. In table 5 the differences between the results of continuous analysis and analysis

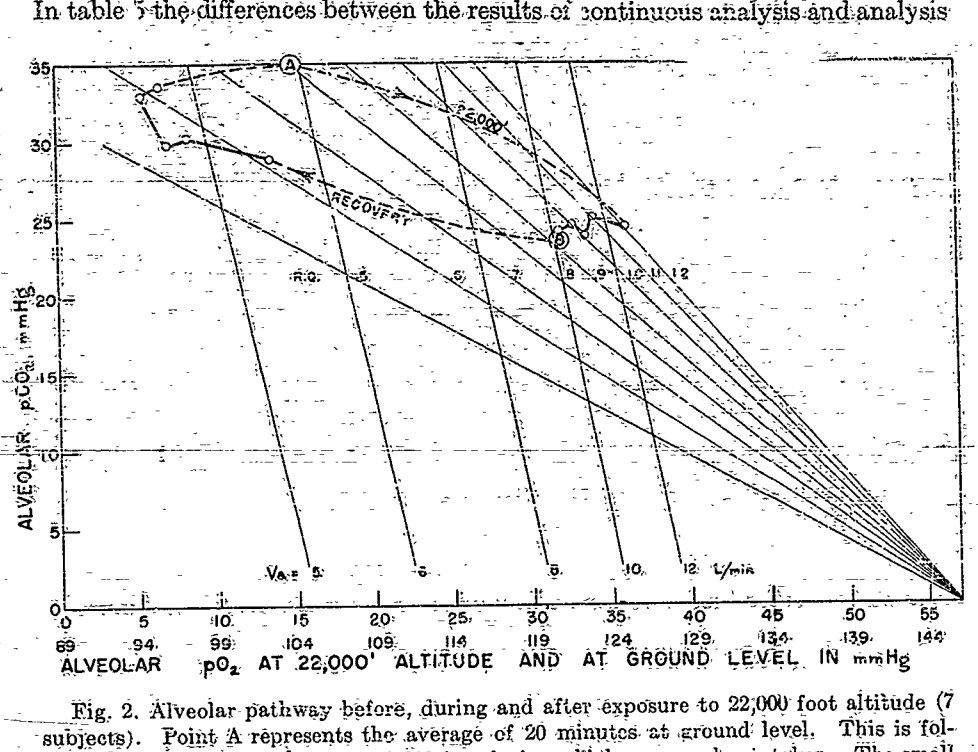

Fig. 2. Alveolar pathway before, during and after exposure to 22,000 foot altitude (7 subjects). Point A represents the average of 20 minutes at ground level. This is followed by a five minute ascent to 22,000 feet during which no record was taken. The small circles are consecutive five minute averages after arrival at 22,000 feet. B represents the end of thirty minute exposure and beginning of descent. No record was taken during five minute descent. The small circles during the recovery cycle are again averages of consecutive five minute intervals during the first twenty-five minutes after arrival at ground level. (Alveolar Ventilations are calculated but agree well with observed Total Ventilation Values.)

of end-expiratory Haldane-Priestley samples are compared. Of particular interest is the fact that the discrepancy between the two methods becomes less as the altitude increases. This may be due to the increasing ventilation rate. Another point of interest in comparing the continuous samples with the forced expirations is that the per cent saturation of the arterial blood estimated from the alveolar pCO_2 and pO_2 with the nomogram of L. J. Henderson (1928) agrees more closely with oximeter readings when the values obtained from forced samples are used (table 6). The values from the continuous method consistently give percentage saturations which are higher than the oximeter readings.

The reproducibility of measurements by continuous sampling is indicated by a comparison of the data of series III and III A, both of which represent normal respiratory behavior of our subjects at 18,000 feet. The results of the two series appear not to be significantly different.

TABLE 5

The discrepancy between the continuous and the conventional methods of alveolar air analyses at various altitudes

(1) ALTITUDE	(2) n	(3) MEAN pCO_2 DIFFERENCE	(4) S.D.	(5) MEAN pO_2 DIFFERENCE	(6) S.D.
Ground Level	112	2.00	0.18	4.06	0.46
12,000	98	2.20	0.17	3.71	0.27
16,000	41	2.38	0.22	3.80	0.53
18,000	121	1.61	0.14	2.95	0.21
20,000	32	1.38	0.19	2.76	0.56
22,000	21	0.83	0.25	1.80	0.31

The meaning of the columns is as follows:

(1) Simulated altitude in feet. (2) The number of comparisons. (3) The mean difference (mm. Hg) in values for alveolar pCO_2 obtained by the two methods. (The continuous method always gives the lower values.) (4) The standard deviation of (3). (5) The mean difference (mm. Hg) in values for alveolar pO_2 obtained by the two methods. (The continuous method always gives the higher values.) (6) The standard deviation of (5).

TABLE 6

Comparison of values for percentage saturation of arterial blood estimated from the two methods of sampling alveolar air with those given by the oximeter

ALTITUDE FEET	CONTINUOUS SAMPLER			FORCED EXPIRATION			Oximeter Hbo_2
	pCO_2	pO_2	Calc. Hbo_2	pCO_2	pO_2	Calc. Hbo_2	
	mm. Hg	*mm. Hg*	*per cent*	*mm. Hg*	*mm. Hg*	*per cent*	*per cent*
12,000	34.8	51.0	87	37.0	47.3	85	86
16,000	29.3	44.7	84	33.7	40.9	79	80
18,000	26.8	41.3	82	28.4	38.3	79	77
20,000	25.1	37.3	79	26.5	34.5	75	75
22,000	24.3	33.4	74	25.1	31.6	69	67

2. *The Effect of Glucose on the Alveolar Pathway.* The flights of series VI and VII were performed to test the effects of glucose ingestion on the alveolar pathway at 12,000 and at 18,000 feet. Previous work on the effect of carbohydrate ingestion on respiratory behavior has been reviewed by Ivy, Friedman and Grodins, 1944. Beneficial effects of carbohydrate diets in high altitude flights were reported by these authors as well as by King et al. (1945a), (1945b), Barach et al. (1945) and others.

If the figures in series VI and VII are plotted on a chart like figure 1 and the resulting graphs are compared with control values (series I and III or III A respectively) it is evident that at 12,000 feet glucose had a slight effect. At

18,000 feet, however, the R.Q. and pCO_2 were both definitely elevated. This confirms the theoretical expectations although the pO_2 was, if anything, somewhat diminished rather than increased by the glucose. If the sugar had been taken slightly earlier the result might have been even more definite. The result is attributable to an increased metabolic R.Q. as well as increased CO_2 liberated from bicarbonate by increased blood lactate.

3. *Work at Ground Level and Altitude* (series IX and X and table 4). The work output per minute was calculated at 49.4 kgm. This is the equivalent of 23.9 cc. of oxygen burning food with a respiratory quotient of 0.831. The calculated extra oxygen consumption required for this work was 277 cc./min. at ground level and at 16,000 feet altitude giving a net efficiency of 8.6 per cent. At both pressures the alveolar oxygen pressure dropped 4 mm. Hg during the work period

TABLE 7

Comparison of observed and calculated ventilation ratios in muscular work

GROUND LEVEL	ALVEOLAR VENTILATION	VENTILATION RATIO	
		OBSERVED	CALCULATED
	L/min.		
Rest	6.34	1.0	1.0
Work	10.61	1.67	2.31
16,000 FEET			
Rest	8.70	1.37	1.23
Work	14.15	2.23	2.99

The V.R. was calculated by Gray's equation:

$$V.R. = 0.4\,pCO_2 - 14.21 + \frac{105}{10^{0.038\,pO_2}}$$

The constant 14.21 was used instead of 15 to make the ground level resting value = 1.0 with a pCO_2 of 37.9. Data for pO_2 and pCO_2 are in summary in table 4.

while the carbon dioxide increased. This change is sufficient to account for the decrease in oxygen saturation of the blood. The calculated oxyhemoglobin saturation parallels the observed ear-oximeter readings.

The values of the alveolar ventilation are calculated in table 7 for rest and work at ground level and 16,000 feet using the summary data in table 4 and a dead space of 210 cc. It is evident that the same work requires an increment of 5.45 liters/min. at altitude and only 4.25 at ground level. This fact was also observed by Gray (1945). All these ventilation rates are reasonably well explained by the use of Gray's equation as given in table 7. The observed and calculated ventilation ratios listed in table 7 increase in the same order and the numerical values are not grossly different. This shows that the recorded changes in alveolar pO_2 and pCO_2 are consistent with the measured ventilation rates.

4. *Heart Rate Changes During Exposure to Simulated Altitudes.* Heart rates were measured in the above flights to obtain some measure of the circulatory stress involved. With the exception of the 12,000 foot value, which seems to be

out of line with the rest of the data, the rate increases progressively with altitude. At the highest altitude (22,000 ft.) it is 127 per cent of the ground level rate.

The rates obtained during the flights following glucose ingestion are considerably higher than the corresponding values for the normal series (except at 12,000 ft.). An increased heart rate as a result of the glucose would not be surprising, since Boas and Goldschmidt (1932) found that the heart rate tends to be higher after a meal than before. Grollman (1929) found that the cardiac output is likewise higher after the ingestion of food.

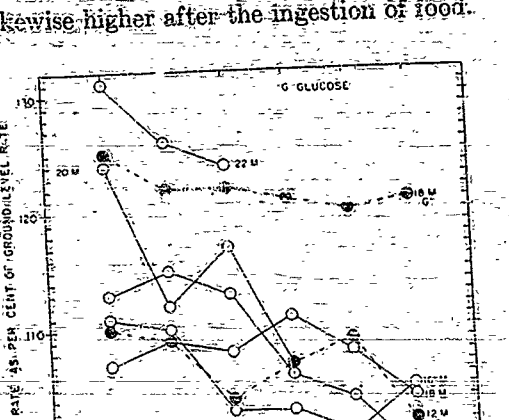

Fig. 3

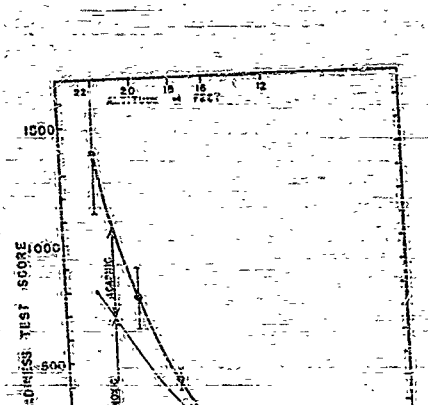

Fig. 4

Fig. 3. Heart rate as affected by time at altitude.
Ordinates: Heart rate as percentage of ground level rate.
Abscissae: Time at altitude in minutes.
Open circles: Data from series I–V (normal series).
Closed circles: Data from series VI and VII (glucose series).
Fig. 4. Steadiness test score as related to alveolar oxygen tension and altitude.
Ordinates: Steadiness test score as percentage of ground level score (mean of eight subjects).
Abscissae: Scale at bottom: Alveolar pO_2 in millimeters of Hg.
Scale at top: Altitude in thousands of feet.
The vertical line through each point indicates the standard deviation of the mean.
The lower of the two curves represents the score expected from anoxia alone, and was constructed by the method referred to in the text.

The change in heart rate with time at altitude is of interest. Figure 3 shows that the rate is, in most cases, highest during the first 10 minutes at altitude. During the time of exposure it tends to drop progressively. In the 12,000 foot series it had returned to the normal ground level rate by the end of the hour. This tendency of the heart rate to return toward the normal with time has been observed previously by McFarland (1938). It may represent a part of the adaptation process of the body to low oxygen tensions. It would be of interest to know whether it is accompanied by an increase in the stroke volume or in the coefficient of utilization.

5. *Performance on the Hand Steadiness Test during Exposure to Altitudes.* Results of the steadiness tests which were administered in flight series I–V are summarized in figure 4. The mean of all scores at each altitude is plotted against the mean alveolar oxygen tension. A barely significant change in score occurs at 12,000 feet. At the higher altitudes the score grows progressively worse. The standard deviation of the mean score also increases with altitude.

An estimate has been made as to how much of the deterioration at each altitude is due to anoxia and how much to acapnia. This was done by the method described in a previous report for the construction of a pure anoxia curve (Otis, Rahn, Epstein, and Fenn, 1946). The acapnic component was estimated by the use of figure 6 of the report just cited. The result of this analysis is shown on figure 4, and indicates that a major part of the deterioration is due to anoxia. At the higher altitudes the acapnic fraction becomes significant, however.

The ingestion of glucose appeared to have no significant effect on steadiness test performance. The scores for the glucose flights at 12,000 and 18,000 feet are almost identical with the scores obtained in the normal flights at these altitudes.

6. *Inspired Carbon Dioxide at 16,000 Feet.* The effect of addition of 6 per cent carbon dioxide to the inspired air at altitude is well illustrated by figure 5. On this diagram is plotted the time course of change in alveolar composition during the experiments of series VIII. (For data see table 3.)

During the initial ten minute period of normal air breathing at 16,000 feet, the alveolar R.Q. is always above 1.0 but steadily drops as does the alveolar pO_2. The ventilation also gradually decreases. With the introduction of 6 per cent CO_2 in air the alveolar pCO_2 rises by about 10 mm., and the R.Q. drops because CO_2 is being retained by the body. This rise in pCO_2 is accompanied by an increase in ventilation which, in turn, results in a gain of about 4 mm. oxygen tension in spite of the high CO_2. For a theoretical discussion of this phenomenon see Fenn et al. (1946) or Gray (1944). By the end of 10 minutes of CO_2 breathing the R.Q. has risen to a normal level of 0.85 indicating the approach of a new steady state.

Attention should be called to the fact that upon addition of 6 per cent CO_2 to air the inspired O_2 tension at 16,000 feet is reduced by 5 mm. Hg. If the inspired O_2 per cent had been kept at 20.9 per cent the addition of 6 per cent CO_2 would have resulted in an alveolar oxygen gain of 5 mm. Hg above that observed and would have resulted in an increased oxyhemoglobin saturation of 3 per cent. However, from a practical standpoint, the substitution of the same volume of O_2 for CO_2 would increase the inspired O_2 to 25.6 per cent representing a gain of 17 mm. Hg in the alveolar air without the concomitant hyperventilation.

During the recovery period on air the reverse changes occur and at the end of 10 minutes the alveolar composition is about the same as immediately before the introduction of CO_2. Had the whole 35 minutes been spent on air, the alveolar pCO_2 and pO_2 would probably have continued to drop. The alveolar composition at the end of 35 minutes in the experiments of series II (normal flights to 16,000 ft.) is indicated on the chart by a solid circle.

The lines of equal ventilation, Va, plotted in figure 3 represent only the alveolar ventilation. According to the chart the addition of 6 per cent CO_2 increased the ventilation from about 10 to about 13 liters per minute. In theory these

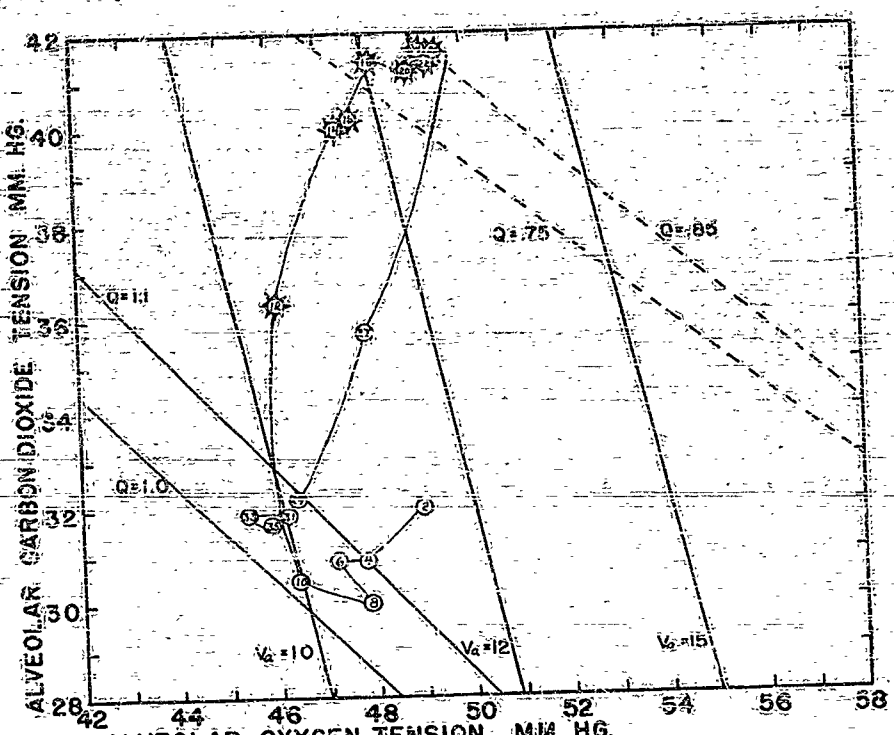

Fig. 5. The effect of 6 per cent carbon dioxide in the inspired air on the alveolar pathway at 16,000 feet.

Ordinates: Alveolar carbon-dioxide tensions in millimeters of mercury.

Abscissae: Alveolar oxygen tensions in millimeters of mercury.

Parallel diagonals: Isoventilation lines for alveolar ventilations of 10, 12, and 15 liters per minute constructed from equation (19) of Fenn, Rahn and Otis (1946) using a value of 346 cc./min. for the oxygen consumption.

Converging diagonals: Lines of constant alveolar R.Q. located by use of equation (6) from the same source.

The solid R.Q. lines apply to air breathing, the broken lines to breathing 6.0 per cent CO_2.

The location of each circle indicates the composition of the alveolar air at the elapsed time in minutes indicated by the number in the circle. Plain circles refer to air breathing, and starred circles to CO_2 breathing. The solid circle indicates the composition of alveolar air at the end of 35 minutes in the experiments of series III.

values apply to any subject at an altitude of 16,000 feet who has an oxygen consumption of 346 cc. per min. The approximate accuracy of these calculated values is indicated by the observed average values in table 4 which show that the total ventilation increased from 12.14 to 15.37 l./min. as a result of the added CO_2. With an assumed dead space of 210 cc. this means an increase of alveolar

ventilation from 10.04 to 12.64 l./min. (cf. 10 and 13). With a slightly greater increase in ventilation the arterial saturation in the 6 per cent CO_2 period would have been greater than in the control but in this case there was on the average no essential change. The large increase in pCO_2 however enabled the subject to attain a higher alveolar pO_2 than would have been possible had he remained longer at the same altitude, breathing air.

SUMMARY

1. The alveolar air composition, ventilation volume, breathing rate and oxyhemoglobin saturation were recorded continuously and heart rate and hand steadiness intermittently on 8 subjects in 83 man flights (a) to altitudes of 12, 16, 18, 20, and 22 thousand feet; (b) to 12 and 18 thousand feet with and without previous administration of glucose; (c) to 16 thousand feet with muscular work, and (d) to 16 thousand feet with the addition to the inspired air of 6 per cent CO_2.

2. The respiratory data illustrate the increase in R.Q. and gradual return to normal during the hour at altitude as well as the subnormal R.Q. and return to normal during recovery. The time course of these changes is illustrated on a pO_2-pCO_2 chart.

3. The increased ventilation at altitude was accomplished by increase in tidal volume only, except at the 22,000 foot altitude. Ventilation was maximum during the first five minutes at altitude.

4. Heart rates showed an immediate increase on exposure to altitude, and dropped toward normal with continued exposure.

5. Hand steadiness showed a barely significant change at 12,000 feet, and grew progressively worse with increasing altitude.

6. The most conspicuous effects of previous glucose ingestion were an increased R.Q. and an augmented heart rate.

7. A given amount of muscular work increased the ventilation more at 16,000 feet than at ground level, but lowered the alveolar pO_2 by the same decrement under both conditions.

8. Addition of 6 per cent CO_2 to the inspired air at 16,000 feet increased the alveolar pCO_2 10 mm. and the pO_2 4 mm.

9. Alveolar samples obtained by the continuous method show a higher pO_2 and a lower pCO_2 than those obtained by forced expirations, but the discrepancy becomes less as the altitude increases.

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MAN'S RESPIRATORY RESPONSE DURING AND AFTER ACCLIMATIZATION TO HIGH ALTITUDE

HERMANN RAHN AND ARTHUR B. OTIS

INCREASED pulmonary ventilation in response to lowered oxygen pressures has long been recognized in man. For a given oxygen pressure, however, this response is not the same for acclimatized and unacclimatized man. In order to analyze the changes which occur during the process of adaptation, various types of experiments have been designed. It is our objective *1)* to describe the difference in alveolar air composition between persons acclimatized to various altitudes and persons residing near sea-level who are acutely exposed to similar altitudes and to predict on this basis the ventilatory acclimatization for any altitude, *2)* to verify this prediction in experiments on 3 subjects acclimatized to an altitude of 9500 feet for a period of 3 weeks, *3)* to describe the respiratory response of men acutely exposed to lower and higher oxygen pressures *after* acclimatization to various altitudes, and *4)* to present data which indicate a greater sensitivity of the respiratory system to CO_2 after acclimatization to altitude.

Difference between Alveolar Air Composition and Ventilation of Acclimatized and Unacclimatized Men at Similar Oxygen Pressures. The alveolar gas composition of permanent residents as well as sojourners acclimatized to altitude have been collected from reports of various mountain expeditions and are presented in table 1. The alveolar respiratory quotient has been computed in each case from the alveolar gas equation (1, 2).

$$R.Q. = \frac{.791\ pCO_2}{.209\ (b - 47 - pCO_2) - pO_2} \qquad \textit{Equation 1}$$

The values obtained by Fitzgerald (24) are not indicated in the table since they cover various altitudes from 4000 to 14,000 ft. on permanent residents of Colorado, U. S. A. The averages of her determinations, however, are incorporated in figure 1 and since only CO_2 determination was made, the alveolar oxygen pressure was computed by the alveolar gas equation, assuming a resting R.Q. of .83.

As far as can be ascertained, all samples were collected during rest, and from a forced expiration following a normal expiration. The samples of Helmholz and Boothby (3), Boothby (2) and Hall and Wilson (4) were taken at the end of inspiration and have been corrected in figure 1 and table 1 to 'end-expiration' samples by adding

1 mm. CO_2 and subtracting 2 mm. O_2 (5). It must further be appreciated that posture changes the resting alveolar gas concentrations considerably. It had to be assumed that all observations in the literature were made in the sitting posture.

TABLE 1. ALVEOLAR AIR COMPOSITION OF SOJOURNERS AND PERMANENT RESIDENTS AT VARIOUS ALTITUDES AS RECORDED IN THE LITERATURE

NO.	ALTITUDE 1000 FT.	BAR. PRES., MM. HG	NO. SUBJECTS	ALVEOLAR			AUTHORITY
				pCO_2	pO_2	R.Q.	
1[2]	0	760	16	38.0	106.0	.858	(3)
2	.55	748	22	38.1	100.7	.797	Our data
3[2]	1.00	733	35	37.7	102.3	.853	(3)
4	4–14		132				(24)
5[2]	6.2	619	32	33.3	79.5	.866	(4)
6	9.2	543	10	34.0	64.0	.828	(25)
7	10.0	525	8	31.5	61.9	.813	(27)
			3	31.5	63.9	.845	
6	12.5	489	10	30.0	58.0	.850	(25)
7	14.0	446[1]	3	25.9	51.6	.776	(27)
8	14.2	458		26.8	53.7	.793	(26)
9	14.2	458	4	27.9	52.6	.807	(18)
10	15.4	429	11	28.0	46.9	.820	(28)
	17.5	401	10	25.6	42.3	.761	
	20.1	356	9	21.4	37.7	.761	
11	21.2	331[1]	2	17.7	42.5	?	(29)
	22.8	310[1]	2	15.6	37.0	.845	
12	22.7	337	1	17.7	40.7	.866	(30)

[1] Based on Altitude-Pressure Tables, U. S. Stand. Atmos. [2] Alveolar values corrected for end-expiratory samples as explained in text.

TABLE 2. AVERAGE ALVEOLAR AIR COMPOSITION OF 22 MEN EXPOSED TO VARIOUS SIMULATED ALTITUDES IN A LOW-PRESSURE CHAMBER. SAMPLES WERE TAKEN EVERY 10 MIN. DURING AN EXPOSURE WHICH LASTED ON THE AVERAGE ONE HOUR

ALTITUDE 1000 FT.	BAR. PRES. MM. HG.	NUMBER OF DETERMIN.	ALVEOLAR					
			pCO_2	S.D.	pO_2	S.D.	R.Q.	Alv. Vent. Ratio (calculated)
0.55	748	130	38.1	3.5	100.7	6.5	.797	1.00
12.0	483	117	37.4	3.0	47.6	4.7	.830	1.06
16.0	412	48	31.7	4.7	40.7	6.1	.869	1.31
18.0	370	160	30.3	3.8	36.5	4.5	.905	1.43
20.0	349	36	26.9	4.7	34.3	5.1	.918	1.62
22.0	321	23	24.6	3.7	31.3	4.6	.937	1.81

The acute exposures to low oxygen pressures have been carried out by means of a low pressure chamber. Twenty-two young men were exposed, on the average, 1 hour at various simulated altitudes. By far the greatest part of the data was obtained on 8 men who served as regular subjects in these experiments lasting over 3

months. All of these men participated daily either as observers or subjects and were thus well trained and had complete confidence in their work. This absence of all anxiety is a prerequisite in obtaining reliable and typical respiration responses. Alveolar samples were collected approximately every 10 minutes in the sitting position from a forced end-expiration and analyzed by the Haldane method or by the automatic oxygen and carbon-dioxide analyzers described by Rahn *et al.* (5). The alveolar gas concentrations for the acute exposure to various altitudes are listed in table 2 and represent the average for the whole period of exposure.

When the alveolar oxygen and carbon dioxide tensions are plotted on the Fenn CO_2-O_2 diagram we obtain 2 distinct curves differentiating acclimatized from unacclimatized men (fig. 1). The iso-altitude line on such a diagram is represented by a

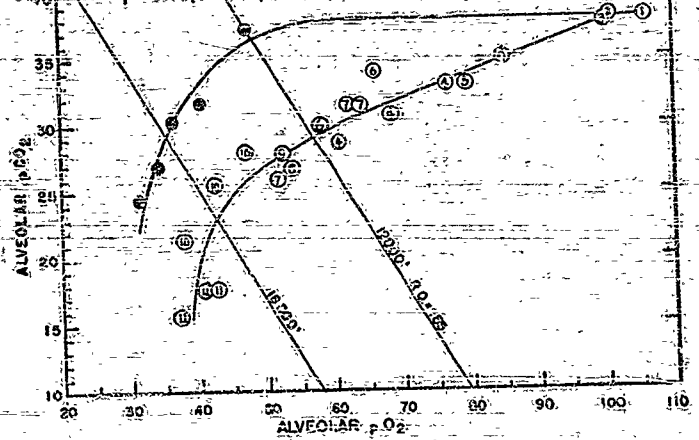

FIG. 1. DIFFERENCE IN ALVEOLAR AIR COMPOSITION between man acutely exposed to various altitudes (solid dots from table 2) and man acclimatized at various altitudes (open circles; the numbers refer to references in table 1). Two iso-altitude lines for a R.Q. = .85 are represented as diagonals.

diagonal the origin of which lies at the inspired oxygen tension for each altitude and the slope of which is determined by the respiratory quotient (1). As an example, the figure includes the iso-altitude lines for 12,000 and 18,000 feet at a respiratory quotient of .85. Any alveolar air or expired air values at this R.Q. must lie on these lines at these altitudes. Under similar conditions altitude diagonals for other pressures lie parallel to those indicated in figure 1.

Two striking facts are revealed: *1*) at a given altitude the alveolar pCO_2 is always lower and the O_2 higher in the acclimatized man; *2*) the alveolar pCO_2 does not fall in the unacclimatized man until an alveolar pO_2 of 50–60 mm. Hg is reached, whereas in the altitude residents the fall begins at approximately 100 mm. Hg, or sea level.

From the alveolar gas concentration the relative alveolar ventilation can be computed from the equation of Fenn (1),

$$V_a = \frac{.864\ X_0 Q}{\text{alv. } pCO_2} \qquad \textit{Equation 2}$$

where V_a equals alveolar ventilation in liters per minute B.T.P.S., X_o equals the oxygen consumption in ml. S.T.P.D., Q, the respiratory quotient, and .864 is a constant. This formula is valid when the inspired air contains no CO_2.

In order to compute the relative alveolar ventilation the assumption has to be made that the resting oxygen consumption is unaffected by the altitude. The value obtained at the common origin of these 2 curves in figure 1 at the alveolar pCO_2 = 38.6 is designated as the *alveolar ventilation ratio* of 1.00. The values taken for calculating the alveolar ventilation curve for the acclimatized men are as follows: the CO_2 is based upon the average curve presented in figure 1, while for the R.Q. the value of .82 was used which represents the average R.Q. for all determinations in table 1.

For the acute exposure the ventilation ratio was computed only from the alveolar values obtained during the last 10 to 20 minutes of exposure where the R.Q. had [illegible]. This makes the R.Q., for our purposes, practically identical with those obtained for the acclimatized people. Thus, for both groups the alveolar ventilation becomes only a function of the pCO_2 and in figure 2 the alveolar ventilation ratio, V_a R., as well as the alveolar pCO_2 can be plotted as ordinates against the alveolar pO_2 and the altitude lines.

Furthermore, the change in serum-bicarbonate of the blood to be expected after acclimatization is completed, can be indicated on the same diagram. If one assumes that the pH upon acclimatization returns to normal (7.40), it follows from the Henderson-Hasselbalch equation that the bicarbonate level likewise becomes a function of the alveolar pCO_2 only.

Figure 2 is particularly helpful in predicting the pathway of the alveolar air composition and alveolar ventilation during the process of acclimatization for any altitude. If we accept these 2 curves, then the process of this adaptation must proceed along a line connecting them. The exact acclimatization pathway, however, is already definitely prescribed by the iso-altitude diagonal as long as the R.Q. remains within normal limits. Thus, for example, the pathways for 5, 10, 15 and 20 thousand feet altitude for an R.Q. of .85 are indicated in figure 2. The acute exposure value after 30 to 60 minutes at these altitudes will lie at the intersection with the unacclimatized curve. The acclimatization pathway will in each case proceed down the altitude diagonal and come to rest at the final intersection with the acclimatized curve. The rate at which this process takes place has been established for the 10,000-ft. altitude and is discussed below. It is of interest to compare the alveolar values obtained by Houston and Riley (8) on 4 men exposed gradually over 4 weeks to increasing altitudes up to 22,000 ft. in a low-pressure chamber. These men never completely acclimatized to any altitude and their alveolar values, described recently in greater detail (38), fall approximately half-way between the 2 curves in figure 2.

The alveolar ventilation curve for acute exposure is of great interest since it indicates no increase in ventilation until the alveolar pO_2 drops to values below 60 mm. Hg. This corresponds to an altitude of approximately 12,000 ft. or to breathing a mixture of 13 per cent oxygen in nitrogen at sea level and is in general agreement with the recent data of Soley and Shock (11), Dripps and Comroe (12) and Rahn and Otis (6) who measured the *total ventilation* at various oxygen pressures. Furthermore, the alveolar ventilation ratios calculated from the extensive alveolar CO_2 and O_2

determinations of Boothby (2) yield values very similar to our own. Thus, it seems quite certain now on the basis of direct measurements as well as calculations based upon the alveolar gas composition that ventilation in man acutely exposed to low oxygen pressures does not increase measurably until the alveolar oxygen pressure drops to about one half of normal (50–60 mm. Hg).

On the other hand, the alveolar air composition of permanent residents or recently acclimatized men indicates a greater than normal (sea level) ventilation. Thus, the hypoxic stimulus is inhibited during at least the first hour in the acutely exposed unacclimatized man. Since below 12,000 ft. altitude this inhibition cannot be due to hyperventilation alkalinity, the only factor that suggests itself is the alka-

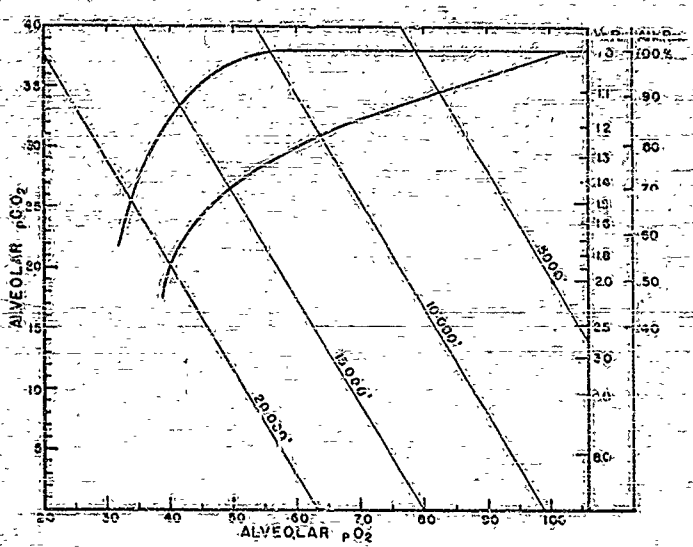

FIG. 2. DIFFERENCE IN ALVEOLAR AIR COMPOSITION and relative alveolar ventilation ratio, V_AR, between unacclimatized man (upper curve) and acclimatized man (lower curve). The calculated change in the alkali reserve, Alk. Res., does not apply to unacclimatized man and applies to the acclimatized man only on the assumption that the arterial *pH* has returned to normal. The iso-altitude lines are constructed for an R.Q. = .85.

linity produced by the lowered saturation of the arterial blood. At 12,000 ft. this amounts to about 0.008 *pH* unit at a pO_2 (alveolar) of 50 mm. Hg and pCO_2 or 38 mm. Hg or an HbO_2 per cent of 86. On the basis of Gray's multiple factor theory this change in *pH* would produce an inhibition of about 16 per cent of the alveolar ventilation which is just about balanced by a 20 per cent ventilation increase stimulus shown in the acclimatized man at this altitude (13).

In order to increase the ventilation, therefore, at this altitude one may speculate that compensatory changes in the blood *pH* must occur bringing the *pH* back to normality before the hypoxic stimulus can effectively exert itself. This is not attained at the end of one hour exposure but appears soon thereafter as will be discussed below.

Acclimatization of the Respiratory Responses Tested at 9500 Ft. During the sum-

mer of 1946 three of us took up residence at the University of Wyoming Science Camp located in the Snowy Range at an altitude of 9500 ft. (B = 535). Prior to this residence daily determinations were made at Rochester, N. Y., to establish the normal alveolar gas concentration, ventilation volume, respiratory rate and breathholding performance tests. Instrumentation was similar to that used in previous experiments (5). All tests were run between 10 A.M. and 12 M. The subject was comfortably

TABLE 3. ACCLIMATIZATION OF SUBJECTS, A.C. AND R.S., AT 9500 FT. ALTITUDE.

DATE	B	ALVEOLAR pCO₂	ALVEOLAR pO₂	ALVEOLAR R.Q.	OXY-ETHE HbO₂%	VENTILATION L/MIN BTPS	BREATHS/MIN	BREATH HOLDING-BREAKING POINT pCO₂	pO₂	R.Q.	HbO₂%	Time held, seconds	EXPOS. TIME	
7-1	744	37.7	101.6	.83		8.58	12.3	49.0	52.9			48		Rochester, N. Y.
7-3	754	38.2	103.6	.84		8.58	11.6	50.1	50.2			51		
7-4	755	38.2	104.6	.85		9.08	11.7	48.9	50.4			53		
7-5	753	38.4	104.2	.86		9.24	13.2	51.0	53.6			54		
7-6	749	37.7	103.7	.85		8.76	12.1							
7-8	533	38.9	57.2	.85	89	7.91	12.6	47.4	30.9		71	34	1 hr.	Wyoming—9500 ft.
7-10	533	34.0	59.9	.77	88	7.45	11.1	41.8	36.9	0.58	68	33	12 hr.	
7-10	536	33.5	59.9	.82		8.63	12.7						18 "	
7-11	536	33.1	63.7	.84	91	9.20	12.3	41.8	40.6	0.64	74	29	36 "	
7-12	536	32.5	61.2	.77		8.48	12.7	40.3	36.7	0.57		32	60 "	
7-14	536	31.7	62.9	.78	91	8.55	12.9	39.3	39.6	0.59	74	34	84 "	
7-15	536	30.6	62.3	.74	91	8.67	13.3	38.8	40.6	0.59	75	35		
7-16	535	30.6	63.9	.77	90	9.10	13.0	39.0	42.2	0.61	75	36		
7-18	535	31.0	63.3	.77	90	8.03	12.7	38.4	43.0	0.60	77	28		
7-21	538	30.7	63.8	.75		8.65	12.5	38.4	42.5	0.59		29		
7-22	535	31.8	62.9	.76	89	9.35	12.8							
7-28	538	31.9	63.8	.80	88	8.96	10.9	40.0	40.0	0.58		30		
Averages on three subjects A.O., R.S. and H.K. before and after acclimatization														
Before	751	38.0	103.2	.84		8.68	11.5	49.7	54.7	0.48		58	Roch.	Wyoming
After	536	30.9	63.3	.76	90	8.51	11.5	37.9	44.7	0.61	77	29	5th to last day	

seated and the alveolar air continuously analyzed. When after 10 minutes or longer the alveolar gas concentrations had stabilized, the values were recorded every minute for 5 minutes and averaged. During this period the ventilation volume and breathing rate were automatically recorded on paper tape and averaged. This procedure was followed by 2 breathholding tests (see below). Two days prior to leaving for the mountains similar tests were made in our high-altitude chamber at the end of 1 hour exposure to an altitude of 9500 ft. This acute exposure as can be seen in table 3 showed no change in the alveolar pCO_2 or ventilation as had been predicted.

Twelve hours after arrival at the altitude camp the test was repeated until the end of the 3-week stay. These data are based largely upon 2 subjects, since the third had to set up equipment in advance and was partially acclimatized at the time the tests could be started.

Table 3 indicates that the CO_2 had already dropped nearly halfway to its final value at the end of a 12-hour exposure and plateaued off at the end of 4 days at this altitude where it remained constant. This progression is shown on the O_2–CO_2 diagram in figure 3 and follows the predicted course except for the low R.Q. values. Not only was the pathway as predicted during the process of respiratory acclimatization, but also the final values after acclimatization fell exactly upon the predicted

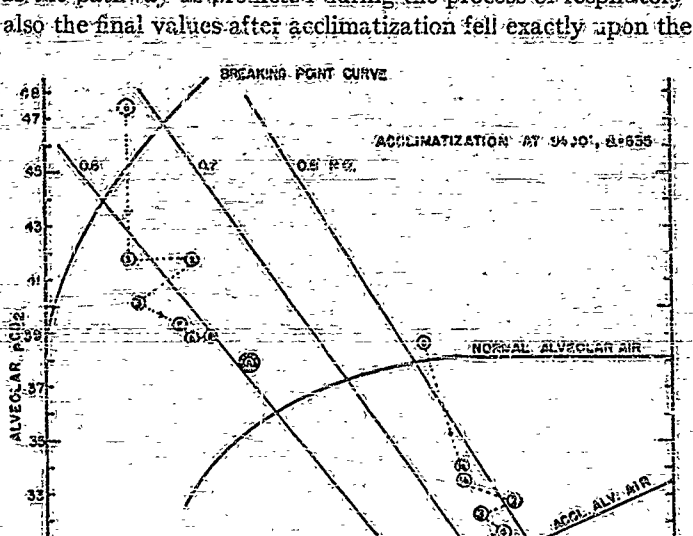

FIG. 3. NORMAL AND BREATH HOLDING BREAKING POINT alveolar air composition (dotted line) of 2 subjects during acclimatization at 9500 ft. The numbers in the circles indicate the days of residence at this altitude. The number 0 indicates 1 hour exposure and R the 5–18th day. 'A' indicates the average for all 3 subjects after respiratory acclimatization was complete. The 2 alveolar air curves (solid lines) are based on figure 2, while the breaking point curve is based on previous data (19) shown also in figure 7.

CO_2 level. Precisely the same change was recently observed by Hetherington, Luft and Ivy (14) when they reported an average difference of 7 mm pCO_2 after acclimatization to 10,200 ft.

The fall of the alveolar R.Q. from an average of .84 to .76 (table 3) is of great interest. Although we have no satisfactory explanation, it should be pointed out that Hasselbalch and Lindhard (15) made similar observations during their 17-day stay at an altitude of 10,800 ft. Very recently the studies of Hetherington, Luft and Ivy (14) have confirmed these observations on 27 men who were taken from an elevation of 750 ft. to a 10,200 ft. level for a period of 2 weeks. The alveolar R.Q. was altered from an average of .80 to .75. Upon return to near sea level they observed a very slow return to the original value.

On the basis of the change in the alveolar pCO_2 and R.Q. before and after acclimatization (last column, table 3), the predicted increase in alveolar ventilation should have been 38/31 × .76/.84 or 11 per cent above the Rochester value provided that the resting oxygen consumption remained unaltered. Actually no significant change was observed. This could most easily be explained by a lower resting oxygen consumption at altitude. However, the studies and review of the literature by Lewis, Illif and Duval (16) indicate no change in basal metabolism in a comparison of 15 independent studies ranging from sea level to 7000 ft. In our subjects the number of breaths per minute was not altered, nor was there any appreciable change in the blood saturation as measured by the Millikan oximeter from that obtained during acute exposure at Rochester.

Averages for all 3 subjects at Rochester and after completion of respiratory acclimatization at Wyoming are given at the bottom of table 3. The rate of pulmonary

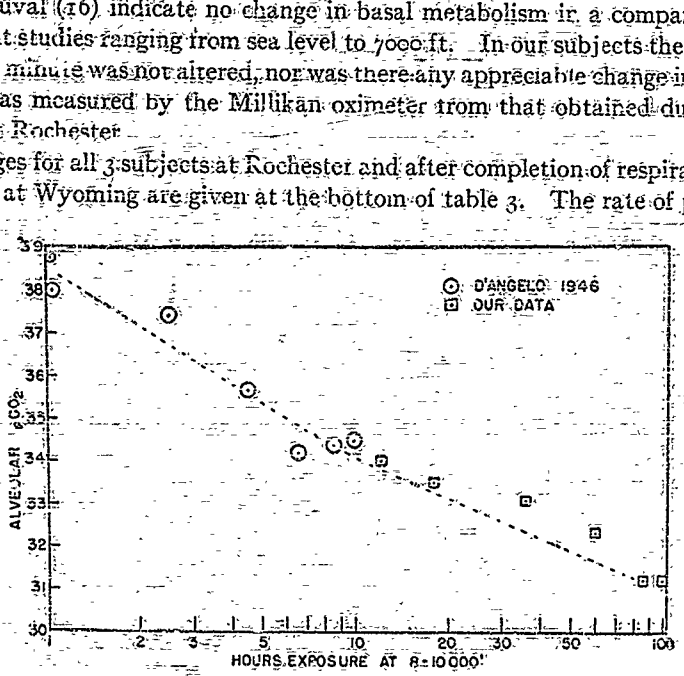

FIG. 4. RATE OF CHANGE of the alveolar pCO_2 during acclimatization to an altitude of 8000–10,000 ft.

adaptation is best visualized in figure 4, in which the alveolar CO_2 level is used as the index of acclimatization. This is completed by the end of 90 hours at this particular altitude. The rate must be governed by the degree of alkalinity incurred from the hyperventilation and the rate of base excretion from the kidneys. Our studies which start after 12 hours are well supplemented by those of D'Angelo (17) who exposed a large number of men in a high-altitude chamber to altitudes of 8 and 10 thousand feet for 10 hours. Although the alveolar gas was not determined directly in his studies, the CO_2 can readily be calculated from the ventilation equation, since all the pertinent data were given, if one assumes a constant dead space. Thus, a fairly complete picture of the rate of acclimatization is obtained for the first time, since other expeditions were always forced to spend several days at various intermediate altitudes and thus became partially acclimatized before reaching their final destination.

Respiratory Response of Man Acutely Exposed to Lower and Higher Oxygen Pressure after Acclimatization to Various Altitudes. The only extensive data are those of

Hall and Wilson (4) who acclimatized 32 subjects to an altitude of 6200 ft. at Colorado Springs. These subjects were then exposed to various altitudes in a low-pressure chamber and their alveolar gases analyzed. Our data extend these observations to 9500 ft. where we breathed a mixture of 12 per cent oxygen in nitrogen after acclimatization (table 4).

The breathing of high-oxygen mixtures after acclimatization causes no immediate change in the alveolar pCO_2 and consequently no decrease in ventilation (table 4). This is in agreement with the recent work of Houston and Riley (8) who found that their subjects after being acclimatized to 22,000 ft. maintained their high ventilation and low CO_2 value after being brought back suddenly to the relatively high-oxygen pressure of sea level. It would seem that re-acclimatization to sea level must occur slowly by retention of base in a similar process, but in reverse to that described above,

TABLE 4. RESPIRATORY RESPONSE TO 100% AND 12% OXYGEN AFTER ACCLIMATIZATION TO 9500 FT. ALTITUDE

INSPIRED GAS AT 9500 FT.	SUBJECT	NORMAL ALVEOLAR RESPONSE			BREATH HOLDING BREAKING POINT			
		pCO_2	pO_2	Oximeter	pCO_2	pO_2	Oximeter	Seconds
100% oxygen	A. O.	31.7		100	46.9	442[1]	100	90
	R. S.			100	51.2	437[1]	100	74
	H. R.	32.9		100	53.5	436[1]	100	173
	Average	32.3		100	50.5	438	100	112
11.77% oxygen in nitrogen	A. O.	25.2	32.8	68	30.3	23.8	58	19
	R. S.	22.6	37.9	78	27.7	28.3	64	25
	H. R.			74	29.4	30.5	67	14
	Average	23.9	35.3	73	29.1	27.6	63	19

[1] pO_2 values obtained by subtraction.

as demonstrated many years ago by Douglas *et al.* (18) upon their descent from Pike's Peak.

Figure 5 attempts to summarize the alveolar response of man exposed to various oxygen tensions after acclimatization. The solid line represents the alveolar values of the acclimatized individual as seen in figures 1 and 2. Point *A* is the sea level value and the dotted curve originating at this point is the acute response to low and high oxygen pressures. Point *B* is the alveolar value for man living at Colorado Springs at 6200 ft. and the dotted line again indicates the alveolar response when acutely exposed to lower oxygen pressures (4). Point *C* is the acclimatized point for approximately 10,000 ft., while the dotted line through this point indicates the response to lower as well as higher oxygen pressures. Similar curves could be drawn for other altitudes and the approximate alveolar response predicated as well as the ensuing acclimatization pathway. Thus as an example, if a man living at Colorado Springs were suddenly placed at an altitude of 18,000 ft. his alveolar pathway would start at *B*, jump to the intersection of the 18,000 ft. diagonal with the alveolar curve (dotted line) originating at *B*. From there it would travel down the 18,000 ft. altitude diag-

onal to its intersection with the acclimatized curve (solid line). On the other hand, if returned from 6200 ft. to sea level his alveolar pathway would travel from *B* on the dotted line to the right until it intersects the sea level diagonal and from there proceed slowly upward to point *A*.

Increased Sensitivity of the Respiratory System to CO_2 after Acclimatization. *A) CO_2 inhalation.* The first experiment measured the ventilation response to CO_2 added to the inspired air. The percentage composition of the various gases inhaled are listed in table 5 and give approximately the same CO_2 tension in the moist inspired

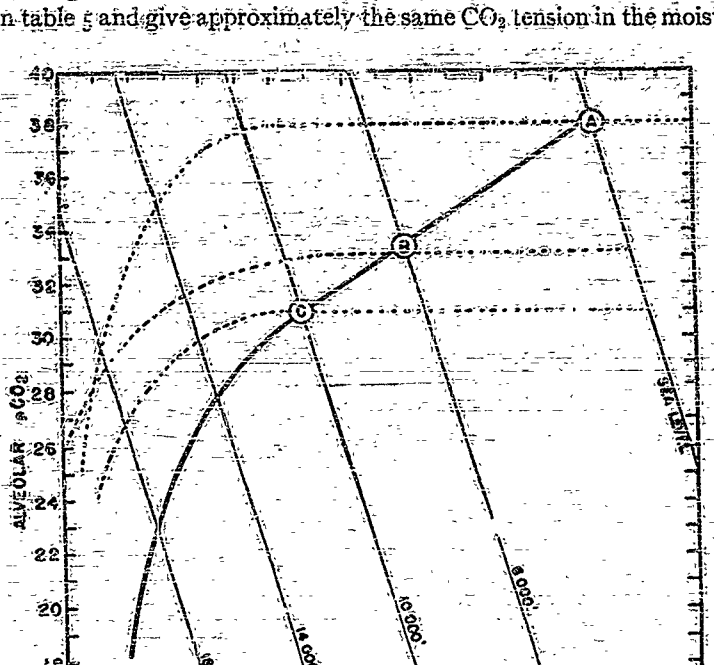

FIG. 5. ALVEOLAR AIR COMPOSITION of the acclimatized man (solid line) and the changes which occur (dotted line) when man acclimatized at sea level, (A); 6000 ft. altitude (B); and 10,000 altitude (C), is acutely exposed to lower or higher oxygen tension. See text.

air at both altitudes. The procedure was such that the subject inhaled consecutively air, low CO_2 and high CO_2 mixture each for 15 minutes from a demand regulator on each gas cylinder. Thus the change could be made instantaneously from one to the other without interruption. Minute to minute recordings were made of the alveolar gas composition, ventilation volume and rate, and ear oximeter. The last 5 minutes of each 15-minute exposure period were averaged. The 3 subjects were run on 2 occasions at both altitudes. The combined averages of all 6 runs are given in table 5.

Although the steady state was not attained with CO_2 breathing, as indicated by the low R.Q., the exposure time in all cases was the same and allows a comparison at

these 2 altitudes. Figure 6 indicates a greater ventilatory response for any given inspired CO_2 tension after acclimatization to 9500 ft. The ventilation increment is approximately 50 per cent greater over the range tested. Although breathing CO_2 increased the alveolar O_2 tension considerably it is expected that this in itself would not influence the response of the respiratory system during an acute exposure (see discussion above). If it did, the higher O_2 tension at altitude would tend to decrease the differences.

The sensitivity of the respiratory system might also be expressed in terms of change in alveolar pCO_2 which will produce a certain percentage increase in ventilation. If this is done for the high CO_2 mixtures at Rochester and Wyoming, we find that after acclimatization to altitude 0.75 pCO_2 induces the same ventilation increase as 1.00 pCO_2 at Rochester.

TABLE 5. EFFECTS OF CO_2 ADDITION TO SAID INSPIRED AIR AT ROCHESTER, N. Y. AND AFTER ACCLIMATIZATION TO ALTITUDE. EACH FIGURE REPRESENTS AVERAGES OF TWO RUNS ON EACH OF THREE SUBJECTS (SEE TEXT).

INSPIRED GAS MIXTURE	INSPIRED pCO_2	ALVEOLAR			OXIMETER	BREATHS PER MIN.	VENTIL. L/MIN. BTPS	VENTIL. RATIO
		pCO_2	pO_2	R.Q.				
Rochester (B = 752 mm. Hg)								
air	0	37.9	104	.86		11.7	8.59	1.00
3.2% CO_2 22.3% O_2	22.5	40.2	135	.75		12.9	14.58	1.76
5.2% CO_2 19.7% O_2	36.6	47.1	126	.75		12.7	23.92	2.78
Wyoming (B = 537 mm. Hg)								
air	0	30.4	65	.77	88	11.1	8.77	1.02
4.5% CO_2 20.6% O_2	22.6	36.4	83	.71	92	12.6	16.98	1.98
7.9% CO_2 20.5% O_2	34.2	41.5	91	.73	95	16.4	33.27	3.88

B) Breath-holding tests. The breath-holding tests were similar to those described by Otis, Rahn and Fenn (19). At the end of normal expiration the breath was held until the breaking point was reached and the alveolar air analyzed. The breath holding time and the ear oximeter reading were recorded. These data are summarized in table 3, while table 4 gives additional data for similar tests carried out breathing 12 per cent oxygen and 100 per cent oxygen after acclimatization was completed at 9500 ft. During the process of acclimatization the composition of the alveolar gas at the breaking point changes in much the same way as the alveolar gas before breath holding. This is shown by the 2 'pathways' plotted on the pO_2–pCO_2 chart in figure 3.

On the basis of the various data in table 3 and 4 the breaking point curve and the normal alveolar curve after acclimatization have been drawn in figure 7 together with similar curves obtained previously on unacclimatized men (19). The vertical

distance between the alveolar air curve and the breaking point curve represents the magnitude of the CO_2 stimulus necessary to achieve the breaking point for a given oxygen tension. Thus this distance may be regarded as measure of the sensitivity of the respiratory center to CO_2.

One can readily see that the vertical distance between these 2 curves is much greater at Rochester than after acclimatization to 9500 ft. (B = 535). At the right hand side of the graph CO_2 is the only factor concerned in achieving the breaking point, oxygen having no effect. Thus near sea level it takes a difference of about (65–38) 27 mm. Hg CO_2 to reach the breaking point while after acclimatization to 9500 ft. at the identical oxygen pressure a difference of 18 mm. Hg (50–32) is sufficient. If we regard the breaking point as an expression of ventilation response (the same at both altitudes) then it is obtained by a change of $\frac{1}{27}$ or .67 pCO_2 at 9500 ft. as compared with $\frac{1}{27}$ or 1.00 pCO_2 near sea level. This figure agrees reasonably well with the relative stimulus of .75 obtained with CO_2 inhalation (test described above).

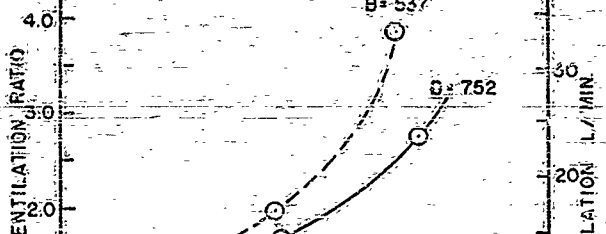

FIG. 6. EFFECT OF THE INSPIRED CO_2 TENSION upon the total ventilation at sea level and after acclimatization to altitude. For details consult table 5.

From the CO_2 dissociation curve one may estimate the CO_2 content of the oxygenated plasma at a pCO_2 of 38 mm. Hg and a pH of 7.4 to be 55 vol. per cent. If we assume that after acclimatization to 9500 ft. the pH returns to normal, then the CO_2 content is reduced to 44 vol. per cent at a pH of 7.4 and a pCO_2 of 31 (breathing pure O_2). Under these conditions the computed pH at the breaking point for both altitudes is the same, namely 7.25. Thus under these conditions of breath holding with pure oxygen where oxygen lack does not enter as a stimulus it is very tempting to regard pH as the determining factor at the breaking point. Furthermore, the increased sensitivity of the respiratory system to CO_2 after acclimatization might merely be the effect of this gas on the reduced buffering capacity of blood and tissues. This of course would also explain the continuation of hyperventilation when man acclimatized to altitude is suddenly exposed to higher than normal oxygen pressures.

C) Breath-holding time. From the above discussion it should follow that when a man acclimatized to various altitudes breathes pure oxygen and then holds his

breath, the breath-holding time is simply a function of his alkali reserve. Thus, from figure 2 one can estimate an alkali reserve reduction to about 50 per cent of normal at 10,000 ft. while the breath-holding time on pure oxygen in 2 of our subjects (*R.S.* and *H.R.*) was reduced to 70 per cent. Unfortunately, no further data are available.

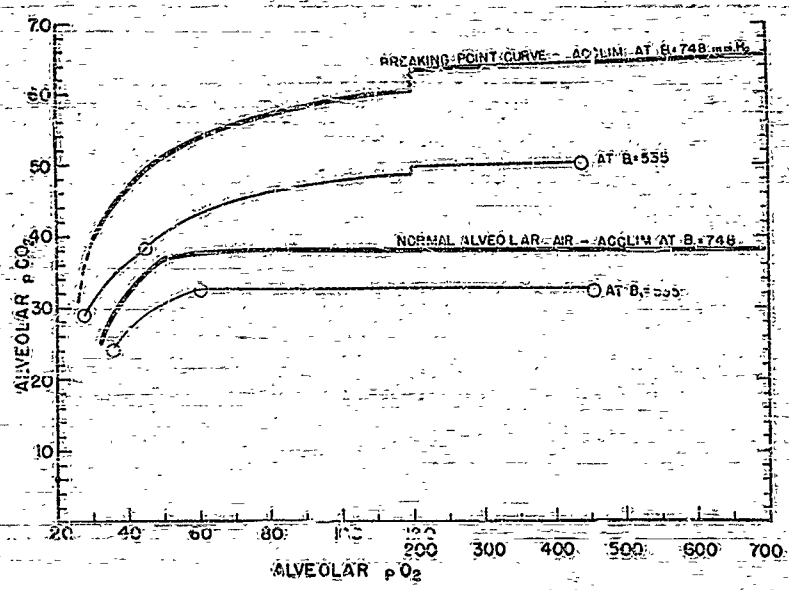

FIG. 7. NORMAL ALVEOLAR AIR COMPOSITION and that obtained after breath-holding when man is exposed acutely to various oxygen tension. The heavy lines pertain to man acclimatized near sea level, the light lines after acclimatization to 9500 ft.

TABLE 6. BREATH-HOLDING TIME AT ALTITUDE (PERCENT OF SEA LEVEL VALUE)

EXPOSED ACUTELY[1]							ACCLIMATIZED							
Authority	No. of subj.	Altitude × 10³ Ft.					Authority	No. of Subj.	Altitude × 10³ Ft.					
		0	5	10	15	18			0	6	7	9.5	14	16	21
Engel et al (31)	40	100	82	68	59	54	Schneider (20)	1	100	55			33		
Rodbard (32)	80	100	94	76	72	56	Hingston (34, 35)	1	100		62		58	31	22
Otis et al (19)	8	100	81	66	59	54									
Brown (33)	212	100				58	Our data	3	100			50			
Average (not weighted)		100	86	70	63	56									

[1] The values at these particular altitudes were in part obtained by interpolation of the data.

When breathing air, however, the breath-holding time is in addition affected by the hypoxic stimulus. Even so the decreasing buffering capacity during the process of acclimatization should exert itself by reducing the breath-holding time as was long ago observed by Schneider (20). Table 6 attempts to summarize the recent investigation of breath-holding time during acute exposure to low oxygen. These data are in

very good agreement and are plotted in figure 8. When this curve is compared to the relatively few breath-holding data known for acclimatized man (20, 34, 35) a definite reduction in breath-holding time is indicated. This decrease in breath-holding time with acclimatization may to some extent be explained by the reduced buffering capacity but may in part be counteracted by a reduced sensitivity to low oxygen.

DISCUSSION

Experimental evidence and data from the literature are compared and indicate that the alveolar air composition and consequently the ventilation response of the respiratory system differ between acclimatized and unacclimatized man for any altitude above sea level. In general it may be stated that the acclimatized subject has a greater ventilation and consequently a lower pCO_2 and a higher pO_2 compared to an unacclimatized individual exposed acutely for one hour to the same altitude.

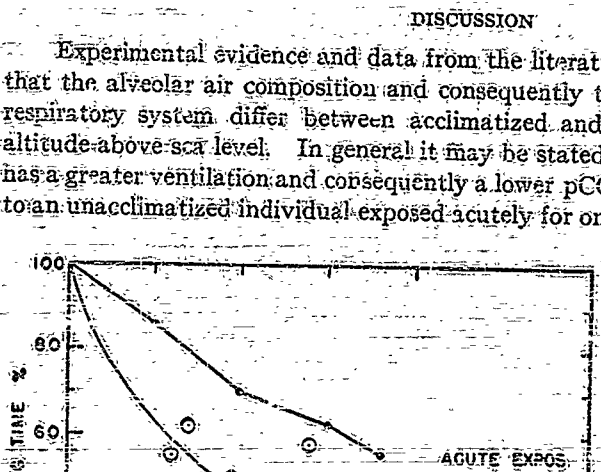

FIG. 8. BREATH HOLDING TIME as a function of altitude in man acutely exposed and acclimatized. Data taken from table 6.

If the rate of respiratory acclimatization is appraised by the alveolar CO_2 level, then our data indicate that this process requires 4 days at an altitude of 10,000 ft. while the data of Douglas *et al.* (18) indicate at least twice as long at 14,000 ft. This ventilatory inhibition, which is thus gradually overcome during the adaptation process, is most simply explained by the respiratory alkalosis incurred from the hypoxic hyperventilation of the acute exposure. With the excretion of base the *pH* gradually returns to normal during the acclimatization process and the ventilatory inhibition is gradually diminished.

Direct and indirect (from alveolar air composition) measurements of the ventilation indicate no measurable change until man is acutely exposed to altitudes above 10,000 to 12,000 ft. At this altitude the alveolar and arterial pO_2 tensions are between 50 and 60 mm. Hg. This is the approximate threshhold response described by Schmidt and Comroe (21) for the chemoreceptors in dogs. On the other hand, v. Euler, Liljestrand and Zotterman (22), recording the activity of the sinus nerve, place

the oxygen threshhold much higher. This is supported by our curve of acclimatized man which indicates relative hyperventilation as soon as pO_2 drops below sea level values (fig. 2). Thus we must look for an inhibition which temporarily (approximately 1 hour) prevents hyperventilation when man is acutely exposed to altitude less than 10,000 to 12,000 ft. or to equivalent oxygen pressures at sea level. The only apparent change is the desaturation of the arterial blood which brings about a small increase in the arterial *p*H. One might argue that not until secondary compensations take place which return the *p*H to normal level would the hypoxic stimulus be able to exert its effect. That such compensatory changes can occur in a relatively short time has been shown recently by Bjurstedt (23) who measured the *p*H continuously in dogs exposed to low oxygen.

Thus the conflicting views as to the hypoxic threshhold of the chemoreceptor may be reconciled by considering that this hypoxic drive upon the acute exposure up to approximately 10,000 to 12,000 ft. altitude (i.e. 14% O_2 at sea level) can be detected by an increase in action potentials from the chemoreceptor (22) but is masked by the desaturation alkalosis if measured by increase in ventilation volume (21).

However, when alveolar oxygen tensions lower than 50–60 mm. Hg are encountered the chemoreceptor drive becomes enough to overcome the inhibitory desaturation alkalosis and now produces an increased ventilation. The recent findings of Bjurstedt (23) that the chemoreceptor drive is actually potentiated by the resulting arterial alkalosis make it hard to explain the unresponsiveness in man acutely exposed to inspired oxygen tension above 13 to 14 per cent oxygen.

The maintenance of the relative hyperventilation at altitude has generally been attributed to the increase activity of the chemoreceptors. When after an acute exposure to altitude the subject is again returned to normal oxygen concentration the ventilation is immediately reduced to normal and even below normal depending upon the alkalinity incurred under the previous hyperventilation. In fact this subnormal ventilation after a stay at 22,000 ft. may last as long as half an hour (6).

However, if acclimatization to altitude has occurred, then a sudden removal to sea-level oxygen values does not reduce the ventilation immediately. This was long ago observed by Douglas *et al.* (18) and others, and most recently by Houston and Riley (8). Hyperventilation is maintained at sea level and gradually diminishes over a period of several days. This might suggest that after acclimatization to altitude the chemoreceptor activity is reduced and thus removal of the hypoxic stimulus has little effect upon the ventilation. Bjurstedt (23) has recently come to this conclusion in studies on dogs where he was able to differentiate between the centrogenic and chemoreflex control of ventilation during various stages of acclimatization. His findings indicate that the chemoreflex drive is all important during the acute exposure to hypoxia and is actually potentiated by concomitant alkalosis. After secondary compensations set in and return the arterial *p*H to normal, the chemoreflex drive diminishes and the centrogenic drive is supernormal and is largely responsible for the maintained hyperventilation after acclimatization to altitude.

Thus, the respiratory system response, according to this concept, is very similar to that at sea level with the exception that due to the lowered buffer capacity ($BHCO_3$ content) it must, according to the Henderson-Hasselbalch equation, become more

sensitive to equal change in CO_2 as long as the *p*H is considered as one of the stimulatory factors acting upon the centrogenic drive.

Consequently, breathing pure oxygen after acclimatization to altitude or suddenly returning to sea level might reduce part of the already insignificant chemoreflex drive, but any reduction in ventilation will have a profound effect upon the acid-base balance and the immediate fall in *p*H and rise in pCO_2 will stimulate the respiratory center and thus prevent the drop in ventilation. Thus the same factor which operates to maintain a constant alveolar pCO_2 and arterial *p*H at sea level also operates to maintain the same arterial *p*H after acclimatization to altitude. The chemoreceptors play only a temporary part in the acclimatization process to high altitude in producing enough over-ventilation to lower the alkali reserve. Once this has been accomplished and the arterial *p*H has returned to normal, the centrogenic drive is able to maintain this hyperventilation by its greater sensitivity to CO_2, this in turn being merely a reflection of the lowered buffering capacity. On such a basis one may find a ready explanation for the altered response of the respiratory system to inhalation of CO_2, breath-holding time and breaking point concentrations described above. Gray (36), on the other hand, leans toward the idea that prolonged acapnia as seen in altitude acclimatization increase the sensitivity to CO_2 per se, while the sensitivity of the respiratory system to *p*H remains unaltered.

If the chemoreceptor drive is relatively unimportant once acclimatization has been achieved then one should be able to simulate the respiratory responses of an altitude-acclimatized individual by any means which would induce a lowering of the alkali reserves at sea level. This could be achieved by prolonged hyperventilation or ammonium chloride ingestion. The effects of prolonged hyperventilation (24 hours) in a Drinker respirator have recently been reported by Brown *et al.* (37). They show in 3 subjects a considerable reduction in the serum bicarbonate level accompanied by an increased sensitivity to inspired CO_2 similar to the response reported in our observations at high altitude. Furthermore, after leaving the respirator involuntary hyperventilation was maintained for a considerable period as seen also in people returning from prolonged stays at high altitudes. Preliminary experiments in this laboratory have shown that daily ingestion of 15 gm. of NH_4Cl for 3 days reduces not only the breath-holding time but also the alveolar pCO_2 at the breaking point of breath-holding in a manner similar to that observed after acclimatization to 10,000 ft. These experiments suggest, as has been pointed out by others, that a large part of the respiratory adaptations concerned with acclimatization to altitude is concerned with an adaptation to a lowered pCO_2 and a reduced buffer system of the blood which in turn raises the pO_2 tension and also prevents large fluctuations in O_2 tensions which are encountered during stresses such as work or voluntary apnea.

SUMMARY

With the aid of an O_2–CO_2 diagram data are presented which allow one to predict the alveolar O_2 and CO_2 composition as well as the relative alveolar ventilation *1)* when man is exposed acutely to any altitude, *2)* during the process of respiratory acclimatization at any altitude and *3)* when acclimatization is complete. In addition, the alveolar pathways can be predicted and described once man is acclima-

matized to any particular altitude and is then suddenly exposed to higher or lower oxygen pressures. These predictions were in part verified by an acclimatization study carried on at an altitude of 9500 ft. for a 3-week period.

Evidence is presented for a pO_2 threshhold of the chemoreceptor drive of ventilation at approximately 100 mm. Hg. This is observed in the ventilation curve of people acclimatized to altitude. However, in *acute exposures* where the alveolar pO_2 is reduced to 50 to 60 mm. Hg this hyperventilation response is completely inhibited for at least one hour. This inhibition is explained as a result of the *p*H rise due to the decreased oxyhemoglobin saturation. If the alveolar pO_2 in acute exposure falls below 50 to 60 mm. Hg, immediate hyperventilation occurs. Exposures of more than one hour at 9500 ft. result in a lowering of the pCO_2 exponentially with time. Final levels are reached after 3 or 4 days.

After respiratory acclimatization to 9500 ft. the respiratory system becomes more sensitive to CO. This response was tested by breathing various CO_2 mixtures and analyzing the alveolar air after breath holding. Data are presented which show the reduction of breath-holding time during acclimatization to various altitudes. The various findings emphasize that a large part of the respiratory acclimatization to high altitudes is an adaptation to a lowered CO_2 tension.

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Continuous Analysis of Alveolar Gas Composition During Work, Hyperpnea, Hypercapnia and Anoxia

HERMANN RAHN AND A. B. OTIS

ONE OF OUR OBJECTIVES during the last few years has been to describe the dynamics of the alveolar gas exchange as it is altered by hyperpnea, exercise and changes in the oxygen and carbon dioxide concentrations of the environment. Two factors have greatly contributed to this reanalysis of classical respiratory physiology: *a*) a method for the continuous analysis of alveolar air (1); and *b*) the development of an alveolar air and alveolar ventilation equation (2). The presentation of these respiratory data is greatly facilitated by the use of the O_2-CO_2 diagram (2) which allows the simultaneous visualization of oxygen and carbon dioxide concentrations in the lung, the respiratory quotient, the alveolar ventilation and hemoglobin saturation.

METHOD

Since our first description of the continuous sampling of alveolar air we have been able to simplify our method so that this device can be easily constructed and installed into any breathing system (fig. 1). A pump delivers continuously 150 ml/min. of alveolar air (the last 10–15 cc. of each tidal volume) to the automatic gas analyzers. Alveolar air is always present in the upper end of the expiratory tube except during the first phase of expiration. To prevent the dead space air from being drawn into the analyzer the alveolar air content of the balloon is pushed back into the main expiratory tube by the positive mask pressure of expiration. This volume far exceeds the pump capacity during this phase. Upon inspiration the balloon is again filled with alveolar air by the negative mask pressure.

O_2-CO_2 Diagram

Any alveolar value can be represented by a point when the O_2 is plotted against the simultaneous CO_2 tension. The computed respiratory quotients form straight lines originating at the inspired oxygen tension, while the lines of equal alveolar ventilation lie parallel to each other with a slope of $-.209$ if air is breathed. Thus the circle in figure 2 represents an alveolar air concentration at sea level. This automatically fixes the R.Q. as 0.85 and the alveolar

ventilation (if the oxygen consumption is 250 ml/min.) as 4.5 l/min. Any deviation of this point is brought on by alteration in one or more of these factors.

If one goes to high altitude one simply slides the R.Q. and ventilation lines along the abscissa until the origin of the P Q. lines coincides with the new inspired oxygen tension. Thus in addition the simultaneous HbO_2 per cent saturation can be read off, if we assume that there is no appreciable gradient between the alveolar air and arterial blood. These iso-saturation lines are determined from the nomogram of Henderson and Dill. The slope represents the Bohr effect.

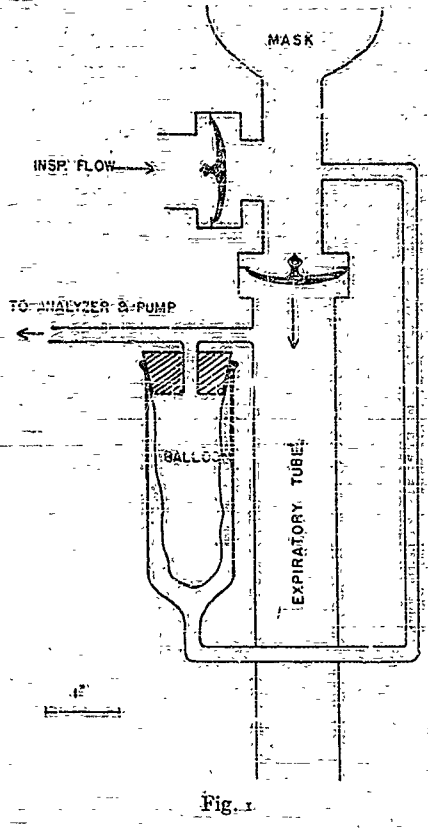


Fig. 1

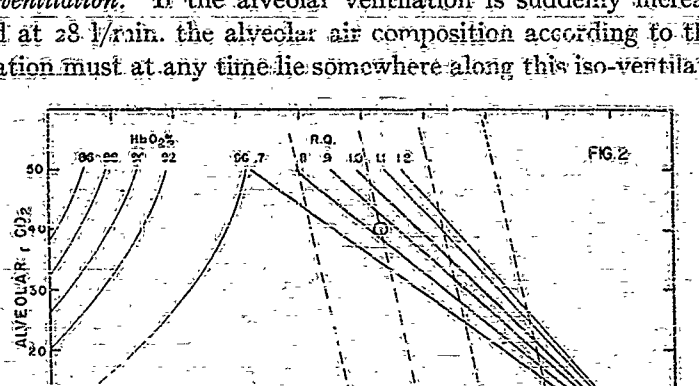
Primary respiratory acidosis and alkalosis pathway. The circle in figure 3 represents an average alveolar air concentration. However, repeated determinations show that this point will vary from time to time as indicated by the normal range. This holds true not only in the resting state but also under strict basal conditions in trained subjects as Carpenter and Lee found many years ago (3). If the breath is held for increasing periods this curve can be extended to the left or after a few breaths of hyperventilation to the right as indicated. Thus acute changes in ventilation affect the gas exchange in a very precise manner largely by alterations in CO_2 output, the oxygen consumption tending to remain constant.

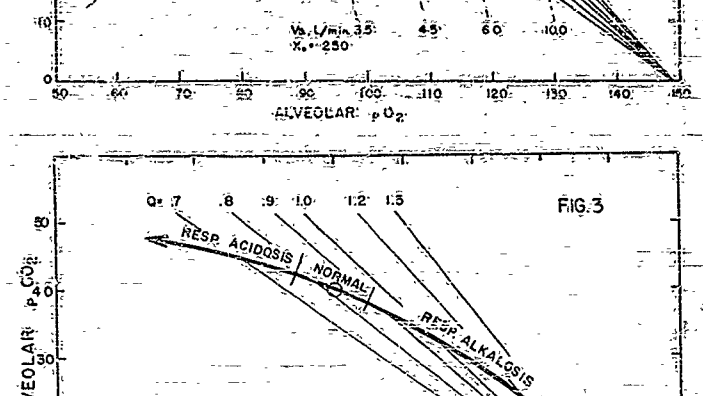
Thus far the initial shift of the normal alveolar air under various conditions (exercise, anoxia, hyperventilation, anesthesia, deadspace increase) has always been observed to follow one of these precise pathways. We might thus refer to these pathways as primary respiratory acidosis and alkalosis pathways which precede the secondary accommodations which will be described below.

It is of interest to speculate here about the so-called unequal gas exchange in the lung. This may be brought about by different ventilation to blood-flow ratios in the various alveoli. A recent theoretical analysis (to be published) supports the concept that the various alveolar gas concentrations that

could exist at any one time in the various alveoli are represented by points lying very close to this pathway, and that when combined they give us a mean alveolar air value represented by the circle in figure 3.

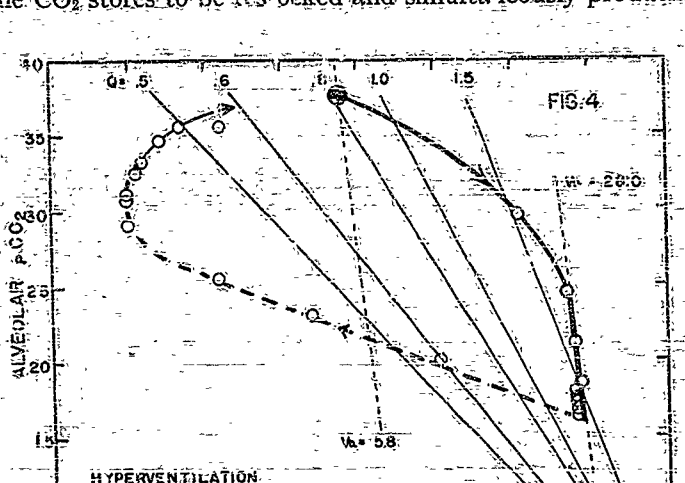
Hyperventilation. If the alveolar ventilation is suddenly increased and maintained at 28 l/min. the alveolar air composition according to the ventilation equation must at any time lie somewhere along this iso-ventilation line.

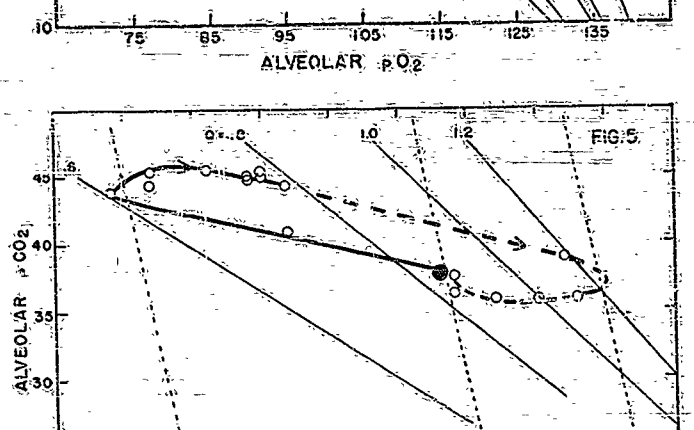




The experimental points in figure 4 show the average readings of 4 subjects. Each point represents an interval of 1 minute from the start of hyperventilation where the alveolar pCO_2 was 37.5 mm. Hg with an R.Q. slightly above 0.8 and an alveolar ventilation of 5.8 liters (solid circle). It can be seen that after the first minute the CO_2 falls off along the iso-ventilation line for 28 l/min. This fall is rapid at first and cuts across the various R.Q. lines. After 10 minutes a pCO_2 of 16 mm. was reached with an R.Q. of about 1.3. If ventilation had been maintained beyond this time the steady state would have

been reached at a pCO_2 of 9 mm. Hg where this particular iso-ventilation line intersects the original R.Q. line of 0.8. The recovery pathway is indicated by the dashed line. The previously incurred alkalosis decreased the ventilation, allowing the CO_2 stores to be restocked and simultaneously producing a very





low alveolar oxygen concentration. Even at the end of 10 minutes of recovery the R.Q. is still below 0.6 and recovery is far from complete.

Thus hyperventilation and recovery are represented by a continuous cycle which is bisected by the normal R.Q. line.

Hypoventilation. An evenly maintained hypoventilation is difficult to achieve in man but it presents the above picture in reverse. We have attempted this by increasing the dead space by breathing through a tube of

about 1300 cc. With such a device the total ventilation is enormously increased, but the alveolar ventilation decreased. The solid circle in figure 5 shows the normal resting value of 3 subjects prior to breathing on this device for 10 minutes. The hypoventilation pathway is likewise clockwise and each open circle represents successive 1 minute intervals. The alveolar ventilation shows an immediate reduction from 6.6 to 4.0 l/min. and then gradually increases and tends to stabilize with an R.Q. of 0.8 and a pCO_2 of 45 mm. As may be seen the original R.Q. was not attained during this period, but as can

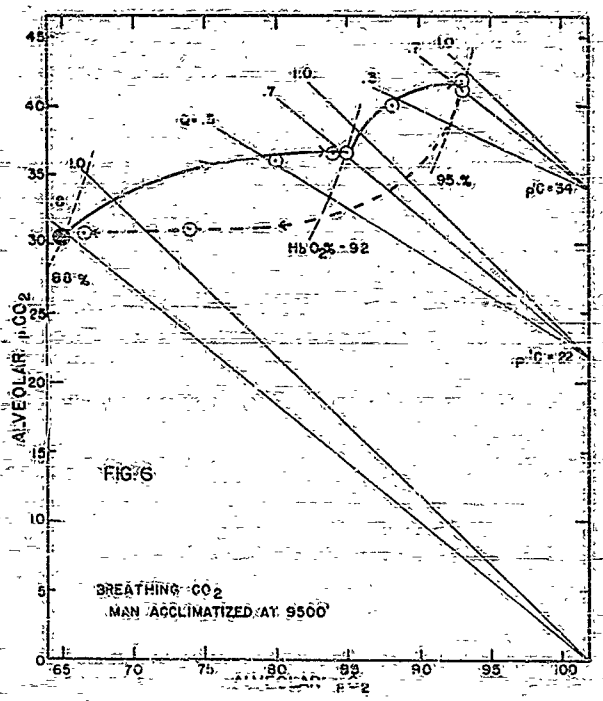


FIG. 6

be predicted from this diagram the alveolar concentrations with further exposures could not have changed very much. Recovery (dashed line) is followed by an immediate rise of alveolar ventilation and high R.Q. indicating that the excess CO_2 stored is now gotten rid of. After 6 minutes of recovery the original equilibrium has been achieved.

Similar pictures have been obtained during intravenous anesthesia by sodium pentothal in man and in dogs. The depression of the respiratory center and the concomitant fall in alveolar ventilation induce the acidosis shift to the left, while recovery from anesthesia is followed by a compensatory high R.Q. (5).

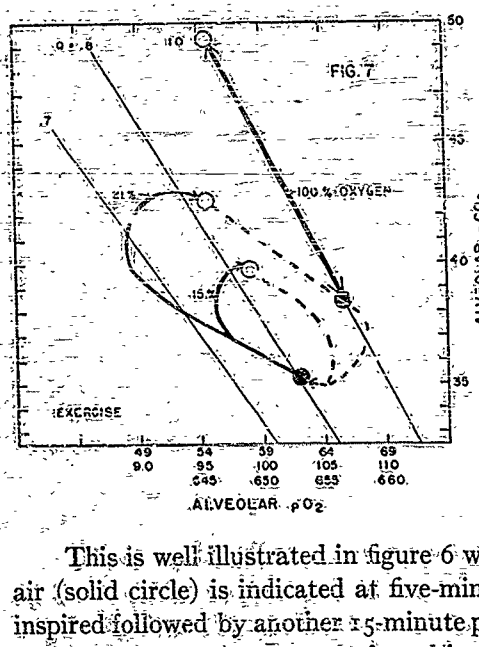
Anoxia

The effects of anoxia have been followed in a large number of individuals in the high altitude chamber (4). The average alveolar pathway for 8 men

exposed for 30 minutes to 22,000′ pressure altitude and the ensuing recovery at ground level has been shown in a previously published figure (*Am. J. Physiol.* 150: 214, 1947). It differs from the previous description of voluntary hyperventilation in that the initially maximal ventilation response is not maintained. Thus the pathway returns to its original R.Q. by a horizontal instead of a vertical line and probably represents a compromise between the anoxic stimulus and the concomitant inhibition by respiratory alkalosis. Data collected at various altitudes indicated that the normal R.Q. or the steady state is obtained in 30 to 60 minutes of anoxia.

CO_2 in the Inspired Air

When breathing air the inspired oxygen tension is approximately divided between the alveolar oxygen and the alveolar carbon dioxide, the exact division depending upon the R.Q. and the rate of ventilation. The same concept can be applied to the extra CO_2 added to the inspired air. Since the respiratory center responds to slight changes in the arterial CO_2 tension by high ventilatory rates the pCO_2 is prevented from rising very much. Thus when breathing CO_2 with the inspired oxygen tension kept as it was before, the gain in alveolar oxygen can be said to equal roughly the inspired CO_2 tension minus the increase in alveolar CO_2 tension brought about by this maneuver.

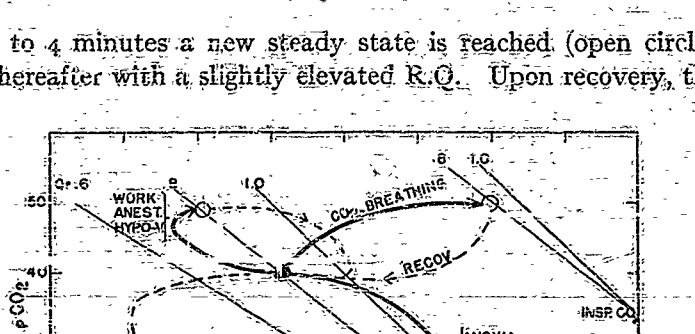


This is well illustrated in figure 6 where the change from normal alveolar air (solid circle) is indicated at five-minute intervals when 22 mm. pCO_2 are inspired followed by another 15-minute period breathing 34 mm. pCO_2. These points represent the average of 3 subjects after three weeks of acclimatization at an altitude of 9500 ft. The inspired O_2 tension was kept identical throughout the experiment. Breathing 22 mm. CO_2 the alveolar CO_2 rose 6 mm. and the alveolar O_2 rose 18 mm. or a total of 24 mm. Hg. With 34 mm. CO_2 in the inspired air the CO_2 and O_2 changed 11 and 26 mm. respectively. Thus at the expense of increased ventilation the alveolar oxygen and oxygen saturation of the hemoglobin (from 88% to 92% and 95%) were greatly increased with relatively little change in alveolar CO_2. Recovery is shown by the dashed line showing the high R.Q. associated with excess CO_2 excretion. The oxyhemoglobin values were obtained from the ear oximeter.

Exercise

The fact that the alveolar CO_2 rises during moderate exercise has been appreciated since the work of Haldane. One might predict that under such circumstances the pathway during exercise would simply proceed up the normal R.Q. line until the new CO_2 level had been reached. However, this was not the case. The lower solid circle in figure 7 represents the normal resting value of 5 subjects. Upon initiation of exercise (20 cm. step, 20 times/min.) a clockwise swing of the alveolar pathway is observed. This is brought about by a relative hypoventilation with its concomitant fall in R.Q. and alveolar oxygen.

After 3 to 4 minutes a new steady state is reached (open circles) and maintained hereafter with a slightly elevated R.Q. Upon recovery, the R.Q.



ALVEOLAR PATHWAYS SCHEMATIC FIG. 8

rises precipitously as has been observed by others. However, the interpretation that this is largely due to CO_2 released by lactic acid is not quite tenable. A good share of it must be the metabolic CO_2 retained during the first part of exercise, which during recovery will be lost in the same way as is the CO_2 accumulation observed with CO_2 breathing, dead space breathing or anesthesia where the lactic acid level is not elevated.

Of further interest is the effect of the inspired oxygen tension upon the exercise pathway. Figure 7 shows the pathway breathing 15, 21 and 100 per cent oxygen. While the subjects and exercise were identical in these three experiments the responses differed considerably. The lower the oxygen concentration the greater the ventilation and the smaller the alveolar pCO_2 and R.Q. change. (With 100% oxygen the R.Q. changes cannot be represented on this diagram and any pathway is limited to the R.Q. = 1.0 line.) This observation suggests that the lower the oxygen tension, the greater the incomplete

breakdown products which in turn produce a greater stimulation upon the respiratory system. Preliminary exercise tests on patients with lung diffusion troubles were studied in collaboration with the Department of Medicine. These patients give a response very similar to normal man under low oxygen tension. In fact, in some advanced cases there is practically no change in the alveolar air during exercise.

Thus these work loops might give a quantitative assay of the respiratory efficiency during exercise. The larger the loops, the more efficient the performer.

SUMMARY

The O_2–CO_2 diagram offers a new approach to the quantitative description of various respiratory phenomena, since it allows the simultaneous visualization of alveolar oxygen, carbon dioxide, respiratory quotient and ventilation. This approach is made particularly useful with the continuous recording of alveolar gas composition. Experiments have been performed which indicate that the alveolar gas concentration can be varied in certain directions only, and along certain pathways. This in a large measure is controlled by the changes in CO_2 output which varied with the relative ventilation. Figure 8 summarizes the principal pathways that have been observed during hyperpnea, anoxia, hypoventilation, exercise and CO_2 breathing as well as the pathways of recovery.

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Normal Variations in End-Tidal Air and Arterial Blood Carbon Dioxide and Oxygen Tensions During Moderate Exercise

MITZI SUSKIND, ROBERT A. BRUCE, MARION E. MCDOWELL, PAUL N. C. YU AND FRANK W. LOVEJOY, JR., with the technical assistance of S. J. VERNARELLI

ALTHOUGH THE CHARACTERISTICS of the respiratory gases have been described for resting normal subjects in relation to the pressure differentials between alveolar air and arterial blood (1–7), there appears to be insufficient data regarding the possible alteration of these pressure differentials during the adaptation to and recovery from a stress such as moderate exercise. Some insight into this problem has been obtained by Lilienthal *et al.* (8) in 1946 who observed the changes occurring with moderately hard work of grade walking (8.8% grade, 3.0 mph). They found the resting pO_2 gradient of 9 mm. (Hg) increased to 16.5 mm. by the 5th to 8th minutes of exercise. Whereas lowering the inspired pO_2 (simulating altitude effects) did not change the gradient, the latter was increased by greater work loads. Appreciable variations were noted in the individual responses to this exercise. These investigators determined the respiratory gas tensions of arterial blood by the micro-method of Riley (9), and calculated the ideal alveolar pO_2, from the observed barometric pressure, inspired oxygen concentration, expired air R.Q. and arterial pCO_2 (10). This procedure is theoretically valid during a steady state of metabolic demand (rest or exercise). Galdston and Wollack (11) studied the changes in the respiratory gases during the first minute of recovery from exercise of 600 to 1200 kg. m/minute intensity. They determined the alveolar air composition by means of the Haldane-Priestley technique (end of forced expiration). Under these circumstances the resting pCO_2 and pO_2 of alveolar air were 1 mm. Hg lower and 1 mm. Hg higher than the corresponding values for arterial blood, respectively. During the first minute of recovery from exercise they found the alveolar pCO_2 and pO_2 to be 3 and 5 mm. higher than the arterial tensions.

Other investigators have studied the effects of altitude, in addition to exercise, on the arterial oxygen saturation. Barcroft (12) found desaturation of the blood when work was performed at an altitude of 14,200 feet. Similarly, Gemmill (13, 14) also observed arterial unsaturation by means of an oximeter with subjects working at the rate of 1555 to 4980 foot-pounds per minute at sea level.

There are a variety of methods for estimating alveolar gas composition, and comparative studies have shown the degrees of agreement between the several approaches in normal subjects during rest (15). Whereas it may be possible to calculate the ideal alveolar pO_2 during a steady state in normal subjects according to the concept of Riley (10) and alveolar equations of Fenn (16), there may be some objections to this approach during unsteady states of adaptation, as well as abnormal situations such as presented by patients with pathological lesions of the lungs or circulation. In order to provide normal standards for the evaluation of respiratory gas gradients in abnormal subjects, it became necessary to make *direct* observations of the composition of alveolar air and arterial blood with the least possible interference in breathing. Accordingly, the automatic alveolar air sampler of Rahn (17) was utilized to obtain end-tidal portion of each expired breath continuously. This air sample is the terminal portion of expired air, and although it does not correspond with the Haldane-Priestley sample, (because the expiratory reserve air volume is not forcibly expressed from the lungs) it has been considered to be a close and satisfactory representation of alveolar air in normals (18). Because of the marked regional inhomogeneity of alveolar air composition which may be observed in abnormal situations such as emphysema (19), one of the authors ($R.\ A.\ B.$) has in earlier publications referred to this end-tidal sample as the 'mid-capacity air,' corresponding to the nomenclature of partitioning of lung volumes (20). This air sample now seems most appropriately designated as the 'end-tidal' (Rahn)—a simple descriptive term—for it then reflects recognition of the difficulties associated with the concept of alveolar air of variable composition, especially in some pathological subjects. Many factors contribute to the variations in alveolar air composition (despite the theoretical stability afforded by homeostatic mechanisms), such as the distribution factor, variations in alveolar ventilation perfusion ratios, diffusion factor and venous admixture, etc. These considerations do not invalidate the concept of ideal alveolar air composition in normal, or moderately disabled patients, in a steady state of performance.

METHODS

Exercise studies, utilizing a treadmill ergometer, direct-writing electrocardiograph, and continuous ventilation flow and respiratory gas analyzer as described previously (20), were made on 10 normal subjects (8 men, 2 women)

of 22 to 37 years of age under ordinary daily conditions of diet, clothing and ambient room temperature and pressure. Continuous analyses of consecutive end-tidal air samples, obtained by means of Rahn's sampling device, were made with a Pauling oxygen tensimeter and Cambridge thermal conductivity cell for carbon dioxide (empirically calibrated against Haldane apparatus) and corrected for BTPS. (The instrumentation lags were taken into consideration.) The exercise stress was standardized for 10 per cent grade walking at 1.73 mph for a period of 3 to 5 minutes, depending upon success in obtaining arterial blood samples. After a trial walk on the treadmill and preliminary observations, the subcutaneous tissue overlying the right radial artery was infiltrated with one per cent procaine anesthesia. The arm was supported by a metal arm rest with straps. Suitably ground No. 19-gage needles were used. Usually the initial sample was drawn with the subject standing erect, and then exercise was started. Consecutive samples then were obtained during most of each one-minute intervals of exercise and early recovery. The blood samples were collected in heparinized syringes, cooled and analyzed for respiratory gas contents

TABLE 1. END-TIDAL AND ARTERIAL GAS TENSIONS IN NORMAL SUBJECTS IN AN ERECT RESTING POSTURE. (25 OBSERVATIONS)

	pCO_2, mm. Hg	pO_2, mm. Hg
End-tidal	35.6 ± 4.3	106.0 ± 4.1
Arterial	35.8 ± 4.7	100.6 ± 4.8
Mean difference	0.2 ± 1.27	5.4 ± 1.26
P%	>50.0	<.006

by the Van Slyke apparatus (21) and tensions by the Riley micro-method, in duplicate (9). The range of experimental error in duplicate analyses of blood gas tensions, expressed as standard deviations from an ideal value of 0, was ±2.3 mm. for pCO_2, and ±2.6 mm. for pO_2. Plasma pH was calculated from the Sendroy nomogram (22).

Additional data on end-tidal and arterial blood gas values obtained from 8 other subjects at rest are also included in this report.

RESULTS

Respiratory Equilibria in Normal Subjects at Rest. Table 1 presents the results obtained from 25 observations on 18 normal subjects at rest. The mean end-tidal pO_2 was 106 mm. Hg, pCO_2 35.6 mm. Hg, and R.Q. (calculated from Fenn's alveolar-air equation, 16), 0.86. The corresponding mean arterial pO_2 was 100.6 mm. Hg, while the pCO_2 was 35.8 mm. Hg. Hence the average resting end-tidal to arterial oxygen gradient was 5.4 mm. Hg, and the carbon dioxide gradient was −0.2 mm. Hg.

Respiratory Equilibria in Normal Subjects During Exercise. The consecutive average values for the partial pressures of carbon dioxide and oxygen obtained at one-minute intervals during the adaptation to, and recovery from,

a standardized exercise stress in 10 normal subjects are shown in table 2 and figure 1. An increase in metabolic activity, due to exercise, is associated with almost parallel lowering of the pO_2 of end-tidal air and arterial blood. There is

TABLE 2. CHANGES IN END-TIDAL AIR, ARTERIAL BLOOD, VENTILATION, RESPIRATION, AND CIRCULATION IN 10 NORMAL SUBJECTS IN RESPONSE TO 10% GRADE WALKING AT 1.73 MPH. (MEAN VALUES ± STANDARD DEVIATIONS FOR CONSECUTIVE MINUTES OF OBSERVATION)

Condition		EXERCISE				RECOVERY		
Minutes		1	2	3	4	1	2	3
End-tidal pO_2 mm. Hg	107 ±2.5	104 ±6.1	93[1] ±5.2	93 ±4.8	95[1] ±4.3	100[1] ±4.4	110 ±4.1	114[1] ±2.6
Arterial pO_2 mm. Hg	98 ±6.1	93 ±3.9	84[1] ±7.8	86[1] ±5.1	88 ±6.6	95 ±7.5	96 ±4.8	99 ±8.1
End-tidal art. pO_2 gradient, mm. Hg	9 ±4.9	11 ±7.7	9 ±10.0	7 ±6.0	7 ±5.3	5 ±5.7	14[2] ±6.6	15 ±7.1
End-tidal pCO_2 mm. Hg	33.9 ±2.1	36.5 ±3.8	41.5[1] ±4.3	42.9[1] ±4.5	43.5[1] ±4.5	40.8[1] ±4.2	36.0 ±2.5	33.9 ±0.9
Arterial pCO_2 mm. Hg	36.0 ±3.0	37.3 ±2.1	38.8 ±3.4	40.9 ±3.6	41.6[1] ±3.5	38.0 ±4.7	35.4 ±2.5	34.8 ±1.0
Arterial end-tidal pCO_2 gradient, mm. Hg	+2.1 ±3.5	+0.8 ±3.7	−2.7 ±4.2	−1.9 ±4.5	−1.8 ±4.1	−2.8 ±4.8	−0.5 ±3.3	+0.9 ±0.0
Arterial O_2 saturation %	95.2 ±1.9	95.2 ±1.5	93.9 ±2.6	93.9 ±3.0	94.1 ±3.1	96.0 ±1.5	96.1 ±1.6	95.9 ±1.6
Arterial O_2 content, vol. %	18.67 ±1.9	18.67 ±1.4	18.42 ±1.8	18.46 ±1.4	18.63 ±2.1	18.56 ±2.2	19.44 ±1.0	18.34 ±2.6
Arterial CO_2 content, vol. %	48.82 ±3.8	48.99 ±3.1	50.36 ±2.6	49.36 ±4.5	49.34 ±4.5	50.08 ±2.9	46.83 ±3.5	50.98 ±3.3
Ventilation l/min. BTPS	5.28 ±0.94	7.56[1] ±1.16	10.91[1] ±1.74	12.64[1] ±1.61	13.46[1] ±1.94	11.17[1] ±2.46	7.48[1] ±1.38	6.31 ±1.15
Oxygen consumption ml/m²/min. STPD	170 ±34.3	306[1] ±65.4	511[1] ±73.8	580[1] ±68.0	596[1] ±49.3	435[1] ±93.8	234[1] ±15.5	199 ±36.5
Vol. % O_2 absorbed from air (resp. eff.)	4.04 ±.32	5.00[1] ±.67	5.81[1] ±.48	6.70[1] ±1.18	5.57[1] ±.58	4.89[1] ±.79	4.06 ±.29	
Heart rate	92.8 ±12.5	111.0 ±9.6[1]	116.4 ±9.8[1]	119.5 ±9.9[1]	117.0 ±9.7[1]	97.6 ±13.2	90.4 ±10.6	91.1 ±9.6
Oxygen transport ml/m²/min. STPD	1.91 ±.34	2.75 ±.66[1]	4.42 ±.78[1]	4.92 ±.56[1]	5.24 ±.83[1]	4.60 ±2.82	2.75 ±.67[1]	2.27 ±.47

Mean barometric pressure 747.9 mm. Hg. [1] These items show significant differences (P 0.27%) from the corresponding *control* values. [2] Approaches significant difference in comparison with observation of preceding minute (P 0.69%).

simultaneously a small rise in the pCO_2 values. Whereas the mean pO_2 gradient observed in these same subjects prior to the exercise was 9 ± 4.9 mm. Hg, it initially increased to 11 ± 7.7, and then declined to 7 ± 6.0 by the third minute of exertion. The lowest value of 5 ± 5.7 was obtained during the first minute of recovery, and was followed by a significantly larger value of 14 to 15 mm. (P 0.69%) in the subsequent 2 minutes. Corresponding fluctua-

tions in the pCO_2 gradient were less reliable due to greater variability. Associated with these changes, despite marked increments in the minute ventilation volume, was a slight but insignificant decrease in the arterial oxygen saturation ($P > 50.0\%$)[4] during the second and third minutes of walking, followed by an equally slight overshooting beyond the resting value during early recovery.

Inter-Relations of Gradients with Other Variables. The inter-relations of these adaptive changes in the respiratory gas tensions of end-tidal and expired air in relation to the R.Q., and blood gas tensions, plasma pH, whole blood CO_2 content, and oxygen saturation of arterial blood are shown graphically on Fenn's O_2-CO_2 diagram, figure 2 (16). The initial resting pCO_2 values were lower, and pH higher, than usually reported values because of the erect posture,

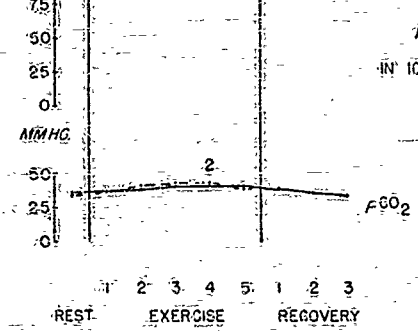

Fig. 1. Average end-tidal air (*broken lines*) and arterial blood (*solid lines*) carbon dioxide and oxygen tensions in adaptation to and recovery from grade walking in normal subjects. Numbers *7* and *2* refer to average pO_2 and pCO_2 gradients during 4th minute of exercise. (Tensions are in mm. Hg, BTPS.)

and the unavoidable effects of minimal apprehension of the subjects about to undergo a unique experience of walking upgrade while being bled from a major artery. The patterns of the air loops are similar to those previously reported by Rahn *et al.* (17). Whereas the adaptative changes in the arterial tensions are considered valid, the observed CO_2 contents, and tensions of the recovery data for the second minute, are open to question. From these data, the initial hypoventilation and hypocirculation (20), relative to the demands of exercise, are accompanied by declines in the arterial pH, increase in CO_2 content, as well as slight hypoxemia.

The relationships of the observed end-tidal to arterial oxygen gradients during exercise are shown in table 3. The magnitude of this gradient varied inversely with the oxygen consumption, minute ventilation volume, tidal volume, physiological dead space, and the oxygen transport per heart beat[5].

[4] Insignificant because of the range of experimental error of the Van Slyke Technique (±0.2 vol. %).

[5] The oxygen transport per heart beat is equal to the product of the stroke volume and the A-V oxygen difference. It is much more nearly related, statistically, to the former ($r = -0.626$

Similar changes were obtained for the pCO_2 gradient, despite a larger coefficient of variation than was found for the pO_2 gradient.

Ranges of Variability in Normal Subjects. Inspection of the data derived from the 10 subjects reveals considerable individual differences in performance. The magnitudes of these variations are reflected statistically in the data of table 2. It was apparent at the time that much of the variability was related to anxiety. In fact, several other subjects were excluded because of arterial spasm which precluded arterial sampling, and in 4 instances vasovagal attacks which culminated in syncope. Of the several factors measured in the 10 subjects included here, the heart rate was the least variable, whereas the ventilation was the most variable.

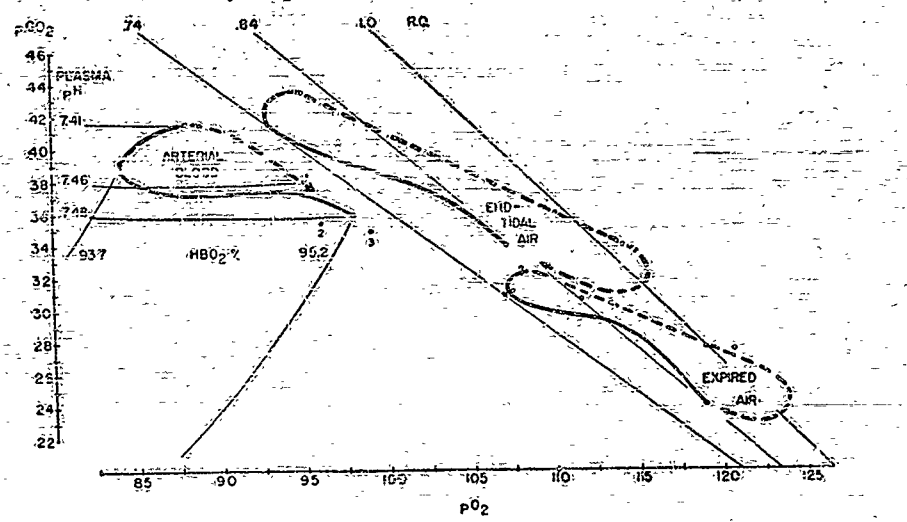

Fig. 2. INTER-RELATIONS OF MEAN CO_2 and O_2 tensions in arterial blood, end-tidal air and expired air in 10 normal subjects during stress of standardized exercise. *Solid circles* indicate resting control observations. *Solid lines* connect consecutive points of exercise, whereas *broken lines* indicate direction of recovery. Small numerals indicate consecutive minutes for early recovery for arterial pCO_2 and pO_2 values. Iso-R.Q. lines arise from inspired pO_2 value. Oxygen saturation lines are derived from oxygen dissociation curve.

In addition to these factors, still other considerations seemed pertinent in accounting for the variation in response. For example, the hemoglobin concentration in these subjects ranged from 11.95 to 16.36 gm. per cent. One of the highest pO_2 gradients was observed in the subject with the lowest level of hemoglobin. Furthermore, rather obvious differences in mechanical efficiency were suggested by the spread of mean oxygen consumption during exercise, corrected for surface area, ranging from 418 to 688 ml. per minute for the same rate of walking upgrade.

± .101, $P < .0001\%$), than the latter, based upon resting measurements utilizing the Fick principle (23). Hence, the relationship between the observed exercise pO_2 gradient and the oxygen transport suggests, but does not guarantee, that the gradient may also vary inversely with the stroke volume.

DISCUSSION

With an average R.Q. of 0.86, the mean end-tidal and arterial pCO_2 values approached 39 mm. Hg in 25 observations of 18 normal subjects in the erect posture at rest. Consequently end-tidal air obtained by Rahn's type of sampling may be considered representative of functioning alveolar air. Under these conditions there was a small pO_2 gradient of about 5 mm. Values of 2 and 0 mm. for CO_2 and O_2 gradients respectively, however, were obtained for the 10 observations at rest prior to exertion (fig. 2). In this instance unavoidable apprehension was apparent in several subjects, which might have been responsible in part for the changes reflected in air and blood values. Lower coefficients of variation for ventilation and oxygen consumption were

TABLE 3. RELATIONSHIPS OF END-TIDAL TO ARTERIAL pO_2 GRADIENT TO OTHER PHYSIOLOGICAL VARIABLES

EXERCISE FACTOR	MEAN S.D.	COEFF. VAR., %	COEFF. CORREL. $r \pm$ S.E.	P %
pO_2 Gradient	9.09 ± 7.2	79.2		
Tidal volume, ml.[1]	1210 ± 536	44.3	−0.659 ± 0.99	<.0001
Physiological dead space[1]	292 ± 153	52.3	−0.656 ± .102	<.0001
Minute ventilation[1]	21.1 ± 5.6	26.8	−0.613 ± 0.110	<.0001
O_2 Consumption[2]	509 ± 48	9.4	−0.52 ± .129	<.006
O_2 Transport[2]	4.41 ± 1.13	25.6	−0.589 ± .115	<.0001

[1] BTPS. [2] STPD/m², body surface area.

observed during the third and fourth minutes of exercise than during the control period (table 2). Hence, despite rigorous attempts to minimize psychological factors from the experimental procedure, the labile effects of anxiety were revealed in the alterations of the respiratory gases subsequent to performing an arterial puncture and obtaining blood samples. Employing continuous sampling methods provides an obvious advantage in the detection of such changes as these.

As a result of the stress of exercise for moderately hard work (caloric expenditure 4 times the resting level), and despite appreciable individual differences, significant lowering of the pO_2 in end-tidal air and arterial blood was observed, along with more transient, but significant elevations in the corresponding pCO_2 values. Simultaneously the gradients fluctuated slightly as ventilation and oxygen consumption increased to meet the demands of the exercise. Proportionately greater changes were observed in the composition of alveolar air, as measured by the end-tidal sampling technique, than in arterial blood. The fact that these data are based upon a less severe stress of exercise, and determined by direct observation of end-tidal air rather than calculating

the ideal alveolar pO_2, may account for the lack of agreement with the findings of Lilienthal *et al.* (8), who found that pO_2 gradient to increase from 9 to 16.5 mm. Hg from rest to exercise. Furthermore, since their exercise stress increased the oxygen consumption by about six times, there may have been a disproportionately greater increase in ventilation than circulation to account for the reported increase in gradient. Although a slight decline in arterial oxygen saturation was observed during early exercise, it was statistically insignificant, despite a significant decrease in the arterial pO_2. This, of course, is an expression of the limits of the Van Slyke technique as well as the characteristics of the oxygen dissociation curve, in that changes at the higher levels are more readily detected by pO_2 than by saturation.

In the experiments reported here, a significant increase in the end-tidal to arterial pO_2 gradient was observed during early recovery, as compared with the last minutes of exercise ($P = 0.69\%$). Since circulation (as reflected in the heart rate) has been found to recover to the resting baseline more rapidly than ventilation at moderate levels of exercise (20), this transient increase in the pO_2 gradient during recovery may be another manifestation of a transient alteration in the effective alveolar ventilation perfusion ratio.

Despite individual variations in each of the respiratory gas values observed *during exercise*, certain trends were apparent which suggested that the magnitude of the pO_2 gradient was dependent to some extent on other physiological factors. Thus this gradient tended to vary inversely with the oxygen consumption, minute ventilation volume, magnitude of either the tidal volume or the dead-space volume and the oxygen transport per heart beat.

In these normal subjects the exercise gradient showed no relationship to the arterial oxygen saturation. In patients with functional disability due to cardio-respiratory diseases, however, there was a significant relationship between the average exercise pO_2 gradient and the arterial oxygen saturation ($r = -0.739 \pm .137$, $P < .0001\%$) (23).

SUMMARY

Twenty-five simultaneous observations have been made in 18 normal subjects of the resting end-tidal air and arterial blood carbon dioxide and oxygen tensions. In the erect posture, the mean end-tidal pCO_2 was 35.6 ± 4.3 mm. Hg, and the mean pO_2 was 106.0 ± 4.1 mm. Hg. Whereas the mean pCO_2 gradient was found to be 0.2 ± 1.27 mm. Hg, the mean pO_2 gradient was 5.4 ± 1.26 mm. Hg. The former value is considered to indicate that end-tidal air is representative of functioning alveolar air.

Simultaneous end-tidal air and arterial blood gas tensions were observed at one-minute intervals in 10 normal subjects just before, during, and early recovery from a standardized stress of treadmill grade walking. Both the end-

tidal air and arterial blood showed almost parallel changes due to exercise, and only in recovery was the mean pO_2 gradient observed to increase significantly. The inter-relationships of these tensions with other physiological data are presented and discussed.

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An Evaluation of Respiratory Depression by Alveolar Gas Changes During Pentothal Sodium Anesthesia.

RICHARD AMENT,† MITZI SUSSIND, AND HERMANN RAHN.

Recent studies of intravenous anesthetic agents, notably pentothal sodium, have placed renewed emphasis on quantitative analyses of physiological changes occurring during anesthesia. The work of Gruber,[1] Gruhzit, Dox, Rowe and Dodd,[2] Beecher and Moyer,[3,4] Moyer,[5] and most recently McCann,[6] contain pneumographic tracings which illustrate the characteristic respiratory patterns produced by intravenous anesthetic agents. Beecher and Moyer[4] have correlated these qualitative studies with minute volume determinations and intermittent blood levels of oxygen and carbon dioxide. Etsten and Himwich[7,8] intensively investigated the reflex responses under pentothal anesthesia and have set forth criteria for determining the stages of pentothal anesthesia. Previous studies have employed

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1 Gruber, C. M., *J. Pharm. and Exp. Therap.*, 1937, **60**, 143.

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the measurement of total ventilation volume as an index of respiratory depression or stimulation. As will be discussed below such measurements may lead to erroneous conclusions when applied quantitatively. Instead, it is here proposed to describe the degree of the effective ventilation in terms of the alveolar gas concentration only, which makes the consideration of volume measurements unnecessary. This method has the further advantage that the alveolar gas concentrations reflect the gas pressures of the arterial blood if corrected for the alveolar-arterial gradient. Suskind[9] has recently shown that during anesthesia this gradient, at least for CO_2, is nonexistent. Thus changes which occur in the pCO_2 of the alveolar air allow one to calculate changes in the arterial pri if the plasma bicarbonates are known.

Method. Alveolar air was automatically sampled by a simple device described by Rahn and Otis[10] and continuously analyzed as previously reported.[11] Readings were made at one minute intervals and the respiratory quotient calculated from the alveolar air equation (Fenn, Rahn, and Otis).[12]

Ventilation volume. The air was expired through a gas meter. Each passing of 457 cc of gas produced an electrical contact which closed the circuit of a magnetic writing pen recording on a constant-speed paper tape.

Frequency of respiration was recorded on the same tape by another pen. The slight negative mask pressure during each inspiration activated a sensitive aneroid which in turn closed the electrical circuit.

Three dogs each weighing approximately 23 kilos were fitted with individually constructed skin-tight masks. After an initial training period alveolar air could be sampled in the unanesthetized animal. Pentothal sodium was then injected into the saphenous vein and all the respiratory phenomena were recorded without interruption. After losing consciousness the dogs were placed in the lateral recumbent position with the head in hyperextension for the remainder of the experiment. Specific attention was placed on the maintenance of an adequate, unobstructed airway by position of the head.

Alveolar gas analyses were also performed in the operating pavilion on 9 patients undergoing elective operative procedures under pentothal anesthesia administered by an intermittent injection technic.

Results. 1. Single injection of 0.5 g of pentothal sodium in dogs.

Three dogs were each given a single injection of 0.5 g of pentothal over a 2-5 minute period with mask in place while continuous analyses were being carried out. Observations were continued until the animal had

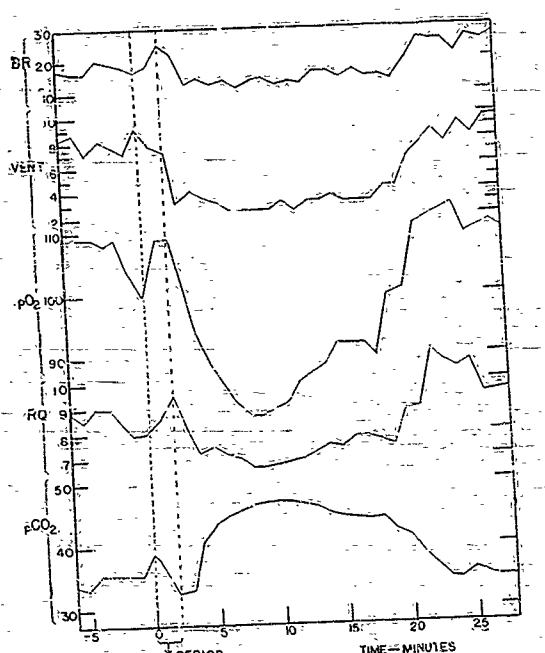

FIG. 1.

Respiratory responses of dog S to 0.5 g. pentothal sodium. Injection occurred between 0 and 2 minutes. BR, breaths per minute; Vent, liter per minute expired at B.T.P.S. (body temperature, pressure and saturated); pO_2 and pCO_2, mm. Hg. alveolar pressure of the gases; R.Q., alveolar respiratory quotient.

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recovered to the point of restlessness, or for a period of 30 to 55 minutes. Maximum respiratory depression was reached in approximately 10 minutes and a gradual return to normal respiratory values followed. Signs of awakening and return of reflexes occurred as the respiratory picture of the animals approached control levels.

A typical record is shown in Fig. 1. It can be seen that the period of maximum depression is attained about 10 minutes after injection. This depression period is characterized by the lowest ventilation volume with its concomitant low pO_2, R.Q. and high pCO_2. The last period of recovery is associated with relative hyperventilation and an R.Q. above normal.

2. Intermittent injection of fractional doses of pentothal sodium.

Two dogs were given intermittent injections of approximately 0.25 g of pentothal sodium until a total of 1 g was administered. These experiments were carried on in precisely the same manner except that the recordings extended over a period of 140 minutes. The same general pattern of Fig. 1 and 2 repeated itself following each intermittent injection.

3. Intermittent injection of pentothal sodium in patients undergoing elective operative procedures.

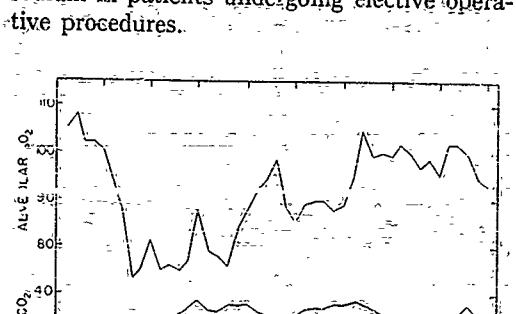

FIG. 2.

Alveolar pO_2 and pCO_2 recorded continuously in a patient before, during and after receiving pentothal sodium intermittently over a 14-minute period. Total dose 1 g. The fluctuations, particularly in the pO_2 level, arise from reflex hyperventilation.

Nine patients undergoing operative procedures were observed. Attempts to obtain control levels of alveolar air in the immediate preoperative period were not totally successful because of the apprehensive state of mind of the patient and the disturbances caused by preoperative medication. During light pentothal anesthesia operative stimulation always produced marked reflex hyperventilation which is reflected in the recorded values (Fig. 2). However, these responses are superimposed upon the respiratory pattern described above as characteristic of pentothal anesthesia in dogs.

Discussion. The question arises of a suitable quantitative criterion for the measurement of respiratory depression. If the total ventilation is used as an index one may make two errors. The first error is produced by changes in the oxygen consumption from the resting, conscious state to the anesthetized state. Thus a reduction of 30% of ventilation is without effect upon the alveolar gas concentration if likewise the oxygen consumption drops by the same amount. The second error is encountered when the breathing rate alters the dead space ventilation. For example a total ventilation of 6 liters per minute may break down into 4 liters alveolar ventilation and 2 liters dead space ventilation (10 respirations of a 200 cc dead space). The same total ventilation can be achieved by 20 respirations of the same dead space and a 2 liter alveolar ventilation. If the former produces a normal alveolar gas composition the latter situation would produce hypoxia and severe acidosis.

Thus unless these entities are known or can be measured the total ventilation may be a poor quantitative index of respiratory depression or stimulation. This is particularly so if one is interested in the effects of the altered ventilation upon the blood and tissue gas tensions.

The next best alternative is to measure *absolute alveolar ventilation* which eliminates the dead space ventilation but is dependent upon the oxygen consumption and for this reason is still unsatisfactory.[12] If respiratory depression or stimulation must be expressed

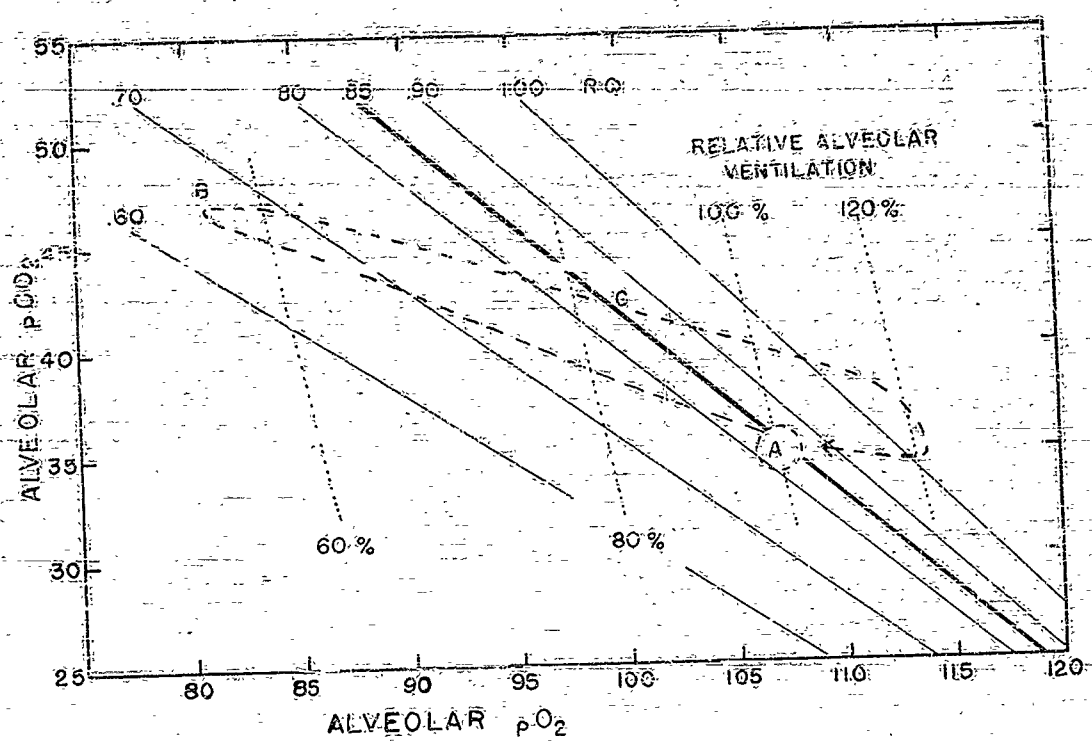

Fig. 3.

Typical alveolar pathway of dog S to single injection of pentothal sodium indicating the simultaneous alveolar pO_2, pCO_2, R.Q., and relative alveolar ventilation. Point A is the average, unanesthetized level prior to injection. Region B indicates the period of deepest depression, region B-C the period of compensation, and C-A the period of recovery characterized by high R.Q. For details see discussion.

in terms of ventilation volume it probably can be most satisfactorily done by calculating the *relative alveolar ventilation* from the alveolar gas concentration. This new derivation is discussed below.

On the other hand the difficulties in the foregoing discussion may be entirely avoided if respiratory depression or stimulation is measured in terms of the deviation it induces from the normal alveolar CO_2 and O_2. Thus the net result of the effective ventilation is expressed without involving the measurement of a ventilation volume. In Fig. 1 the various recorded values are plotted against time. In Fig. 3 the alveolar O_2 and CO_2 are plotted against each other and the whole period of anesthesia is represented by a point moving in a clockwise direction. Each point on such a graph simultaneously determines the alveolar respiratory quotient as well as the relative ventilation index. The iso-R.Q. lines are straight and originate at the inspired O_2 tension while the iso-ventilation lines have a negative slope of .209 when air is inspired.[12] The advantage of this type of graph is that it allows the simultaneous visualization of the various components of respiration.

Point A in Fig. 3 is the average alveolar air composition of the unanesthetized dog just prior to the injection of pentothal. The R.Q. is .85 and the alveolar ventilation is assumed to be normal or 100%. Following the injection, respiration is depressed. This is seen by a rapid fall in the alveolar pO_2 and R.Q. and a slower rise of the pCO_2 until point B is reached. The curve from A to B is very constant in dog and man and has been designated as the "respiratory acidosis pathway" by Rahn and Otis.[10] It is reproducible from time to time and has been observed whenever

the alveolar ventilation is reduced by dead space breathing, anesthesia or voluntary apnea.[10,18]

Point B indicates the deepest depression reached about 10 minutes after the injection and represents the greatest retention of metabolic CO_2 as indicated by the low R.Q. value. Since Suskind[9] has recently shown in this laboratory that there is no significant difference in the anesthetized dog between the arterial and alveolar pCO_2 one may estimate the changes in arterial pH accompanying the pCO_2 rise. Assuming a normal base bicarbonate level of the plasma the Henderson-Hasselbalch equation indicates a pH drop of .12 units between point A and B. Unpublished studies with standard doses of nembutal show much greater depression yielding CO_2 and O_2 values of 50 and 60 mmHg respectively.

This initial respiratory depression is followed by a period of compensation. The CO_2 stores of blood and tissues are slowly adjusted to the new alveolar CO_2 tension and as the rate of accumulation of CO_2 decreases, the R.Q. returns to its original value (Point C). However, the new steady state is not maintained. Throughout the period of compensation, the anesthetic is wearing off, and the sensitivity of the respiratory system to CO_2 is increasing. Thus we see during the final stages of recovery (region C-A) a relative hyperventilation which rids the blood and tissues of the recently acquired CO_2 stores and is manifested by an R.Q. above .85. The 3 respiratory phases described here, depression A-B, compensation B-C, and recovery C-A, all grade into one another and last approximately 10 minutes each. With complete recovery the CO_2 tension in blood, tissues and alveoli are readjusted to the original value of point A and the steady state with a normal R.Q. is observed.

At this time the dog becomes restless, and when an additional injection is given the whole cycle repeats itself. This was accomplished 3 times in succession in one dog and twice in another, the total period of anesthesia lasting over a period of 2 hours. This alveolar pathway cycle is typical not only for anesthesia but also in conscious man when the alveolar ventilation is reduced by various artificial means.

Should it be desirable to express the drug action in terms of a ventilation unit this can be done by assuming that the ventilation is normal (100%) only when it maintains an alveolar concentration of point A, the control value during the conscious state. This unit is called the *relative alveolar ventilation*, which has the advantage that it makes ventilation independent of changes in metabolic rate and thus offers a better physiological comparison for fluctuating metabolic rates as encountered in anesthetic studies.

The *relative alveolar ventilation* of point A is equal to $\frac{k \cdot R.Q. \cdot 100}{alv.\ pCO_2}$ where k is a constant yielding a ventilation of 100% when the values of point A are substituted. (This equation is derived from the alveolar ventilation equation, Fenn[12]). The constant for our example is 41.2. When lines of equal "relative alveolar ventilation" are plotted they form straight lines as indicated in Fig. 3.

It can be seen that the deepest respiratory depression is obtained when the alveolar ventilation is 58% of the ventilation required to maintain the alveolar air composition at point A. Recovery, on the other hand, is associated with a relative hyperventilation reaching a maximal value just over 120%. Fig. 1, however, indicates a much larger relative change in the *total ventilation*, (from 100% to 38%) and is therefore misleading unless the marked drop in oxygen consumption and breathing rate is properly evaluated.

It is obvious from the data that respiratory stimulation or depression is a continuously changing state. This makes a quantitative comparison difficult unless some particular phase of the anesthesia cycle is employed as reference. Since *total ventilation* as an index may be quite misleading it is here suggested that the deviation from the normal alveolar pCO_2, R.Q. and/or *relative alveolar ventilation* be used as a quantitative and physiologically comparable approach to studies of res-

[18] Otis, A. B., Rahn, H., and Fenn, W. O., *Am. J. Physiol.*, 1948, **152**, 674.

piratory depression or stimulation until continuous arterial blood gas analyses become more practical.

Summary. 1. The alveolar O_2, CO_2 tension and R.Q., minute volumes and respiratory rates have been recorded continuously in animals and man under pentothal sodium anesthesia administered by single and intermittent injection.

2. When the alveolar gas concentrations are plotted with the aid of a CO_2-O_2 diagram a typical anesthesia pattern can be shown indicating the regions of depression, compensation and recovery.

3. With intermittent injections of pentothal sodium this typical pattern is repeated.

4. The theoretical significance of this respiratory pattern and its utilization for analysis of quantitative changes in respiration in the study of anesthetic agents is discussed.

Application of Gray's Theory of Respiratory Control to the Hyperpnea Produced by Passive Movements of the Limbs[1]

ARTHUR B. OTIS.

THIS PAPER is an attempt to analyze the hyperpnea produced by so-called 'passive' movements of the limbs in terms of Gray's (1) multiple factor theory of respiratory control. Gray, himself, has made an approximate analysis of this phenomenon, but he did not have available the necessary data to make an exact application of his theory. Analysis of such a situation by this theory requires the following simultaneous information: 1) the alveolar (rather than the total) ventilation and 2) the arterial or alveolar carbon dioxide tension. Previous workers (2, 3) have made measurements of the ventilation but not of the pCO_2, and if there is no increase in metabolism the latter factor can be estimated from the former. On the other hand, if movement of the limbs by external forces involves an increase in metabolism, as is indicated by the experiments of Liljestrand and Stenstrom (4), the pCO_2 must be directly measured.

EXPERIMENTAL

Series I. The subject lay supine on a table which supported the whole body except the right leg below the knee. The right foot was strapped to a stirrup located at the end of a lever, the axis of which was in line with that of the knee joint. The lever could be driven by an electric motor in such a fashion that the lower leg was alternately extended and flexed through about 60 degrees of arc at a rate of 70 cycles per minute. After a 15-minute rest period the

subject breathed oxygen through a mouthpiece from a continuous circuit 12-liter recording spirometer equipped with a soda lime absorber and circulation pump. Continuous recording was made during the subsequent 25 minutes which were divided into 5 five-minute periods as follows: *1*) normal breathing; *2*) passive exercise; *3*) recovery; *4*) passive exercise; *5*) recovery.

Experiments of this type were performed on 9 subjects. A summary of the results is shown in table 1. Only two subjects failed to show an increase in minute volume, and all subjects showed an increase in either volume or frequency of breathing during the exercise periods. All but one subject showed an increase of oxygen consumption during the 1st exercise period, and all showed an increase during the 2nd exercise period.

Series II. Since the above experiments indicated an increased metabolism, it seemed desirable to make measurements of alveolar gases during passive exercise. In a 2nd series of experiments, the subjects breathed air through

TABLE 1. SUMMARY OF EXPERIMENTS IN SERIES I.

PERIODS	1	2	3	4	5
Frequency of breathing	100	150 ± 76	110 ± 28	199 ± 77	117 ± 41
Minute vol.	100	143 ± 42	97 ± 13	140 ± 51	84 ± 19
Oxygen consumption	100	110 ± 11	108 ± 11	120 ± 10	107 ± 16

Column heads designate the consecutive 5-min. periods comprising the experiment: *1*) normal breathing; *2*) passive exercise; *3*) recovery; *4*) passive exercise; *5*) recovery. All values are the averages for 9 subjects and are expressed as percentage of the normal control values. Standard deviations are indicated.

a face mask and expired through a gas meter which recorded the respiratory rate and volume. Alveolar oxygen and carbon dioxide tensions were obtained each minute by means of the automatic alveolar air sampler described by Rahn *et al.* (5). With this device the last few milliliters of each expiration are passed through a Cambridge Instrument Company CO_2 meter and a Pauling Oxygen Tensimeter. Following a 15-minute initial rest period, measurements were made during a 30-minute period consisting of 10 minutes normal, 10 minutes passive exercise and 10 minutes recovery.

Series III. A third series of experiments was similarly conducted except that the subject sat on a bicycle with his feet on the pedals. A motor was coupled to the rear wheel so that each pedal could be driven at a rate of fifty revolutions per minute.

RESULTS

A summary of the average values for alveolar pCO_2, pO_2 total ventilation and frequency of breathing observed in each period of Series II and III is given in table 2.

The results of all 3 types of experiments confirm the finding made by previous workers (2, 3) that movements of the limbs produced by external forces involve a considerable increase in the ventilation. In some individuals there is also an appreciable increase in oxygen consumption. This increased metabolism presumably indicates that the subjects were unable to be completely passive, but unconsciously resisted the applied forces to some degree. However, the simultaneous measurement of alveolar carbon dioxide tension

TABLE 2. AVERAGES OF MEASUREMENTS OF ALVEOLAR pCO_2 AND pO_2, TOTAL VENTILATION, AND FREQUENCY OF BREATHING: ORIGINAL MEASUREMENTS WERE MADE EACH MINUTE DURING THE EXPERIMENT

Period	Subject	Series II				Series III			
		pCO_2	pO_2	Minute Vol.	Frequency of Breathing	pCO_2	pO_2	Minute Vol.	Frequency of Breathing
		mm. Hg		*l/min. BTPS*		*mm. Hg*		*l/min. BTPS*	
Control	*R. S.*	42.5	96.2	5.78	11.3	38.2	102.5	8.29	13.5
	H. R.	39.8	99.6	6.33	8.7	37.3	100.1	7.84	11.4
	I. E.	42.0	95.2	6.32	11.3	36.8	101.7	7.62	13.7
	R. O.	42.3	94.3	5.83	4.9	36.5	106.8	7.79	6.6
	A. O.	39.7	98.8	6.50	8.1	35.5	103.8	8.01	10.1
	R. D.	40.3	96.1	7.37	8.9	40.3	98.6	7.21	12.3
	Mean	41.1	96.7	6.35	8.9	37.4	102.2	7.79	11.3
Passive Exercise	*R. S.*	39.3	104.2	7.32	13.8	37.9	105.8	9.29	15.9
	H. R.	37.7	105.8	7.98	10.1	35.4	103.6	8.63	8.2
	I. E.	40.5	96.7	7.25	13.5	38.2	101.8	10.04	14.4
	R. O.	41.8	94.5	5.67	7.2	41.1	102.6	9.16	7.9
	A. O.	37.6	104.7	8.42	6.3	36.7	115.5	15.67	8.9
	R. D.	36.4	103.9	7.59	11.4	38.2	101.7	12.38	24.9
	Mean	38.8	101.6	7.37	10.4	36.9	104.7	10.86	13.4
Recovery	*R. S.*	40.5	100.9	6.11	11.6	38.3	102.09	7.80	13.7
	H. R.	39.2	96.9	5.33	7.9	37.4	98.30	7.52	10.3
	I. E.	41.7	94.3	5.99	11.6	36.1	103.01	7.19	13.6
	R. O.	41.2	96.2	6.34	7.1	38.1	103.27	7.03	5.5
	A. O.	39.2	94.9	6.00	8.7	34.2	03.70	5.86	8.5
	R. D.	36.5	101.7	6.70	10.6	39.1	100.07	6.84	16.8
	Mean	39.7	97.5	6.08	9.4	37.2	100.07	7.04	11.4

and ventilation makes it possible to estimate by Gray's theory the amount of ventilation due to the H-ion, pCO_2 complex, and the amount due to the passive exercise *per se*, if it is assumed that these are the only respiratory stimuli involved, and that the bicarbonate capacity of the blood remains constant.

According to Gray's theory each of the various stimuli for respiration exerts its own independent effect, and the total stimulus is equal to the algebraic sum of the individual stimuli. In a normal resting individual the H-ion, pCO_2 complex is assumed to be the only stimulus acting. From various se-

lected data showing the ventilatory response to breathing carbon dioxide mixtures, Gray has shown that the alveolar ventilation may be related to the alveolar pCO_2 by the following equation, when the H-ion, pCO_2 complex is the only stimulus for breathing. (Gray's equations require that the ventilation be expressed as a *ventilation ratio*, V.R., which is defined as the actual alveolar ventilation divided by the resting alveolar ventilation.)

$$V.R._{H,pCO_2} = 0.4\ pCO_2 - 15 \qquad (1)$$

The constants of the above equation require the normal resting alveolar pCO_2 to be 40 mm.Hg. (The ventilation ratio, V.R., is unity under such conditions.) Since the resting alveolar pCO_2 of our subjects was not exactly 40, we have adjusted the intercept constant of the above equation. In our second series of experiments the mean resting alveolar pCO_2 was 41.1 mm. The mean alveolar ventilation during the same period was assumed to be due entirely to the H-ion, pCO_2 complex and to have a V.R. value of unity. The new intercept constant was obtained as follows: $1 = (0.4)(41.1) - K$; $K = 15.44$

$$V.R._{H,pCO_2} = 0.4\ pCO_2 - 15.44 \qquad (2)$$

The actual alveolar ventilation was calulated in l/min. for each minute of the experiment for each subject from the observed total minute ventilation, frequency, and an estimated dead space (physiological plus mask) of 210 cc. In order to express the ventilation in terms of a *ventilation ratio*, each of the alveolar ventilation values thus obtained for a particular subject was then divided by the mean resting alveolar ventilation for that subject. A mean *ventilation ratio* for each minute of the experiment was then obtained by averaging all the individual V.R. values for each minute. The mean values are plotted as the solid line of figure 1. That part of the alveolar ventilation theoretically due to the H-ion, pCO_2 complex was next calculated by inserting the mean pCO_2 for all subjects for each minute of the experiment into *equation 2*. The values thus obtained were plotted to form the dotted line of figure 1.

A similar procedure was applied to the data of Series III, and the results are shown in figure 2. The formula used for computing the theoretical alveolar ventilation due to the H-ion, pCO_2 complex in this series was

$$V.R._{H,pCO_2} = 0.4\ pCO_2 - 13.96 \qquad (3)$$

since the mean resting pCO_2 was 37.4 mm. This resting value, which is considerably lower than that obtained in the second series, reflects the well-known effects of posture on the resting alveolar values, since the subjects were supine in the second series and sitting on a bicycle in the third series.

The mean alveolar respiratory quotient and oxygen consumption, as cal-

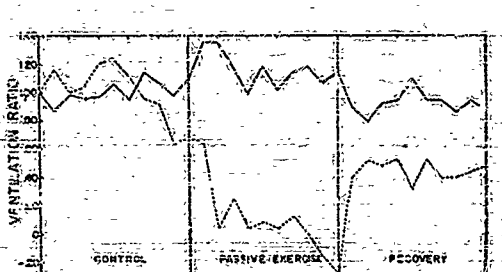

Fig. 1. EFFECT OF LIMB MOVEMENTS on alveolar ventilation in the experiments of Series II. The solid line indicates the actual alveolar ventilation as determined from the total and dead-space ventilations. The broken line indicates the amount of alveolar ventilation caused by the H-ion, pCO_2 complex as calculated from Gray's equation. The vertical distance between the two curves at any time measures the amount of ventilation being stimulated by factors other than the H-ion, pCO_2 complex. For example, at 18 minutes the actual alveolar ventilation is 1.18 in V.R. units (1.18 times the resting alveolar ventilation); the calculated stimulus value for (H,pCO_2) is 0. Therefore all the ventilation is due to some factor related to the limb movements. At 20 minutes the pCO_2 has dropped so low that the calculated stimulus of (H,pCO_2) has a negative value, in other words an inhibition of 0.26 V.R. units. Since the actual ventilation is 1.14 V.R. units, the stimulus from the moving limbs must, according to the theory, be great enough to overcome this inhibition and in addition induce 1.14 V.R. units of ventilation. The stimulus from the moving limbs at this point is, therefore, 1.14 + 0.26 = 1.40.

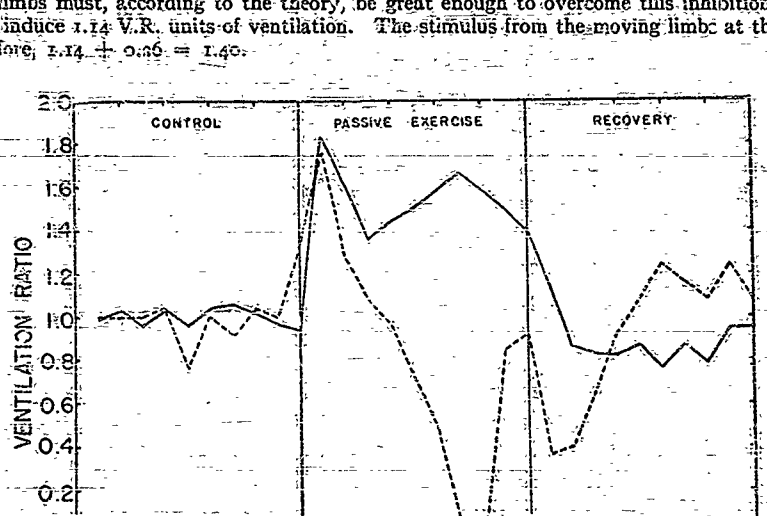

Fig. 2. EFFECT OF LIMB MOVEMENTS on alveolar ventilation in the experiments of Series III. For explanation see the legend for figure 1.

culated by use of *equations* 7 and 17 from Fenn, Rahn and Otis (6), for each minute of the experiments of Series II and III are plotted in figure 3.

The solid line in figures 1 and 2 indicates the actual alveolar ventilation and the dotted line the amount theoretically due to the prevailing H, pCO_2.

The vertical distance between these two curves at any instant represents stimulation or inhibition of the ventilation by other agents, presumably stimuli from the moving limbs. During the control periods of both experiments the alveolar ventilation remains relatively constant, and shows only random variation around a ventilation ratio of 1. When passive exercise begins there is an immediate increase in the ventilation which reaches a peak during the first or second minute. Thereafter, it declines, nearly to the resting value in Series II, but remains well above in Series III.

That portion of the alveolar ventilation theoretically due to (H, pCO_2) during the period of passive exercise is never as great as the actual ventilation

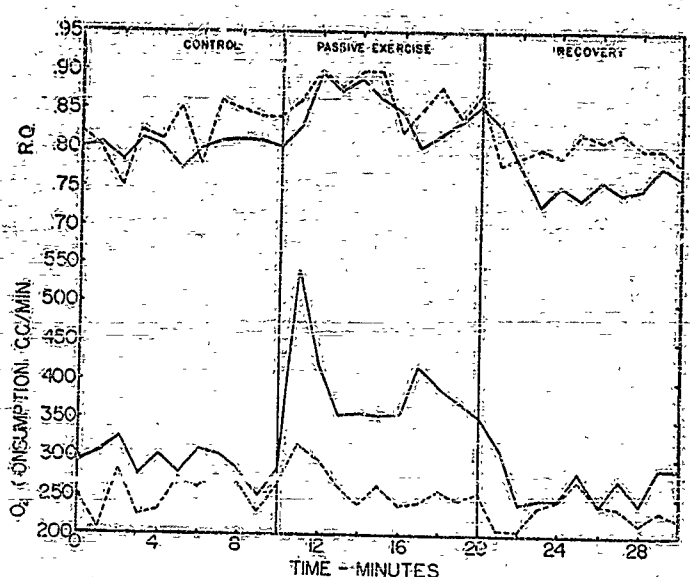

Fig. 3. Oxygen consumptions and respiratory quotients calculated from the data of Series II (dotted lines) and Series III (solid lines).

except during the first minute of exercise in Series III. Although the actual ventilation remains above normal throughout the period of passive exercise, the partial stimulus of (H,pCO_2) becomes in general less and less and declines to a point where it is exerting no effect or is even inhibiting the ventilation. Correlated with this is the generally elevated R.Q. (fig. 3) which indicates the development of hypocapnia during this period. At the same time the stimulus from other agents (presumably something related to the moving limbs) generally increases throughout the period of passive exercise (except during the last two minutes of Series III), as indicated by the divergence of the dotted and solid lines of figures 2 and 3. This stimulus at times exerts an effect great enough to account for an increment of ventilation equivalent to 1.5 times the resting ventilation.

During the recovery period one would expect the ventilation to be due entirely to the H-ion, pCO_2 complex and that the dotted and solid lines of figures 1 and 2 would converge. In figure 2, they do in fact have about the same average value, but in figure 1 they remain somewhat divergent and leave about 0.4 V.R. units of ventilation without explanation, unless one assumes some after-discharge phenomenon or persistence of some chemical agent. The behavior of the R.Q. (fig. 3) during the recovery period is instructive. In Series III it is, on the average, depressed indicating retention of CO_2 and recovery from the hypocapnia that developed during the exercise period. In Series II the R.Q. is less depressed and recovery is less complete.

The increased oxygen consumption observed during the exercise periods of Series I has already been mentioned. The oxygen consumption plotted in figure 3 for each minute of Series II and III shows a rise to a maximum during the first minute of exercise and a subsequent decline to a value that remains relatively constant after the third minute. In Series II this constant value is not significantly different from the resting consumption but in Series III it remains considerably elevated. It may be concluded that in Series III, at least, the limb movements were not entirely passive. The relatively high oxygen consumption during the first minute of exercise may be related to two factors. In the first place, the subject would probably tend to resist the applied force more when it first began than later after he became accustomed to it. Secondly, the movements might improve the venous return from the limbs and drive out blood that had pooled there during the preceding 15-minute rest period and 10-minute control. Such blood would probably be relatively deficient in oxygen and high in CO_2, and when it reached the lungs would cause an increased O_2 consumption as well as an increased alveolar pCO_2. The amount of blood pooled would be much larger in Series III because the subjects were in the sitting position, and it is in this series that the most striking initial increase in oxygen consumption occurs as well as an increase in alveolar pCO_2 (enough to account for nearly all the increased ventilation during the first minute).

Unpublished data obtained by Rahn in this laboratory indicate that when a subject who has been in the erect position on a tilt-board for some time is tilted to the supine position, the oxygen consumption may show an increase of 90 per cent during the first minute, due in part to displacement of blood from the limbs by the change of position. Much the same conditions probably hold in the experiments of Series III except that here the movements of the limbs serve to displace the pooled blood.

COMMENT

In summary, the above experiments indicate that movements of the limbs produced by external forces are not always entirely passive, but that

they may involve an increased oxygen consumption and carbon dioxide production. Furthermore, the possibility that such movements may introduce previously pooled blood into the general circulation must be considered. This effect would be especially important in experiments of only two or three minutes duration, such as those of Harrison *et al.* and of Comroe and Schmidt, because most of the blood displacement would probably occur early in the exercise period. Measurement of the alveolar or arterial pCO_2 is therefore necessary to evaluate the stimulating effects of such movements on the respiration. When analyzed in terms of Gray's theory, the present experiments indicate that the stimulus from some factor associated with the moving limbs is great enough to produce a ventilation increment about equal to the resting ventilation. Gray's estimate of the magnitude of the stimulus from limb movements is about five times as great, but he assumed that there was no increase in metabolism.

The nature of the stimulus from the moving limbs is, of course, not identified by the present experiments, but there is much evidence that it is a reflex involving receptors in the joints (2, 3, 7, 8). The importance of such reflexes during *active* work is not generally agreed upon. Asmussen and Nielsen (9) believe that they are mainly responsible for the hyperpnea during light work, but that during heavy work (in which the blood lactate is increased) some unidentified chemical substance to which the arterial chemoreceptors are sensitive becomes more important. On the other hand, von Euler and Liljestrand (10) conclude that direct chemical stimulation of the respiratory center is the principal mechanism involved. Comroe's (11) opinion that no single factor theory will suffice is well borne out by the available evidence, although at present it is not possible to quantitatively evaluate all the factors involved.

To speculate briefly, perhaps an approach based on the assumption that at least a part of the hyperpnea of muscular exercise as it normally occurs is a conditioned response to a complex pattern of stimulus conditions would prove fruitful.

SUMMARY

The observation of previous workers that movements of the limbs produced by external forces cause an increase in the ventilation rate of human subjects is confirmed. In some individuals an increase in the oxygen consumption was observed, indicating that these maneuvers are not always entirely passive. Continuous measurement of the alveolar oxygen and carbon dioxide tensions made possible the calculation of the ventilatory stimulus due to the movements of the limbs per se by means of Gray's multiple factor theory. Such calculations show that the stimulus from such movements is

enough to produce a ventilation increment 100 per cent to 150 per cent of the resting ventilation.

I wish to make acknowledgment to members of Civilian Public Service unit No. 115-R who served as subjects and technicians during these experiments, to Miss Helen Jacobs for making some of the calculations, and to Dr. Hermann Rahn and Dr. W. O. Fenn for their critical advice.

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METABOLIC CHANGES OF BLOOD AND TISSUE GASES DURING ASPHYXIA[1]

FLORENCE J. HERBER

Recently several investigators (1–4) have questioned the alleged benefits of 5 to 7 per cent CO_2 in oxygen as a resuscitating agent for cases of obstructive asphyxia. The present study was undertaken, first, in order to confirm evidence concerning the acid-base balance of the blood during obstructive asphyxia, and thereby to aid in the evaluation of the CO_2-O_2 mixture as a resuscitating agent in such cases. Secondly, we have expanded that evidence to include a simultaneous study of blood lactic acid levels, (a measure of the degree of metabolic acidosis during asphyxia), and other pertinent variables to be indicated. Thirdly, we have made a preliminary study of the metabolic activity of muscle tissue during obstructive asphyxia. Efforts have been made to correlate it with simultaneous acid-base variations in the blood.

METHODS

The study of 10 healthy dogs, anesthetized by intraperitoneal injections of Dial[2] to surgical anesthesia, is reported here. The trachea was cannulated, and each dog was asphyxiated by rebreathing from a small spirometer a quantity of room air approximately equal to four times its tidal volume. Respiratory excursions throughout the asphyxiating procedure were recorded on a moving drum by a writer attached to the spirometer bell. A 5 cc. alveolar air sample was withdrawn from the rebreathing tube into an airtight syringe every one or two minutes during the asphyxiating procedure. Just before each sample was drawn, the chest was forcibly compressed, and held in this position during the sampling. The syringes were inverted in tubes of mercury, and so sealed until analyzed for CO_2 content within 24 hours by the Fry (5) gas analyzer.

Every one or two minutes during the asphyxiating procedure a 5–6 cc. sample of arterial blood was withdrawn from the carotid artery through a blunted needle into a syringe, the dead space of which had been filled with 6.5 percent NaF. The exact amount of fluoride in each syringe was determined, and this dilution factor considered when calculating blood concentration from the analytical figures. Approximately 6 mgm. of fluoride per cc. of blood was found to be sufficient to prevent clotting and glycolysis for 48 hours, if the blood was stored

[1] Work done under contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Rochester, and under contract with the Air Materiel Command, Wright Field.

[2] Each cc. containing 0.1 gram diallylbarbituric acid, 0.4 gram urethane, 0.4 gram monoethylurea, and q.s. distilled water.

in ice water. The withdrawal and storage of the blood was done without exposing it to air. The CO_2 and O_2 contents of 0.5 cc. arterial samples were measured by the Van Slyke and Neill (6) manometric technique of blood gas analysis. Arterial pH was determined at room temperature by the Beckman pH meter in a capillary glass electrode, without exposure to air. The hematocrit ratios were determined on duplicate samples of arterial blood, centrifuged exactly 20 minutes at 4000 r.p.m. The arterial blood of *dogs 4* to *10* was analyzed for lactic acid, according to the Barker and Summerson (7) technique, and the color concentration read by the Klett-Summerson colorimeter, using a 460 mu filter.

One-half hour before the beginning of asphyxia, the tibialis anterior and peroneus longus muscles in each hind leg of *dogs 6, 7,* and *10* were dissected free, leaving blood and nerve supply intact. The skin flaps were closed to permit the reestablishment of normal gas content of the muscles. Two samples, each approximately 1 gram in size, were cut from each isolated muscle and the two corresponding samples from the other leg at death. The transfer of tissues to stoppered containers of CO_2-free FeF_3 was made as quickly as possible (15 to 20 seconds from the time the skin flap was opened). Muscle CO_2 content was determined by the method of Danielson and Hastings (8), a modification of the Van Slyke manometric technique for blood gas analysis.

Electrocardiographic records (lead I only) were taken for 20 seconds out of every one or two minutes, i.e., at exactly the same time as blood and alveolar air were sampled by assistants in the experiment.

Muscles samples were analyzed within 18 hours after the experiment, and blood samples within 24 hours. The proteins and sugars were precipitated for the lactic acid determination within 24 hours, though completion of these analyses was often delayed up to 72 hours.

No attempt was made to resuscitate the animals, but blood samples were withdrawn as long as the arterial pressure would permit, and alveolar air samples were taken over the same length of time.

RESULTS

The mean values of each variable measured (with the exception of muscle CO_2), as well as their standard deviations, are presented in table 1. There was a wide variation from animal to animal in survival time; the mean figures for each variable therefore have progressively less reliability after the seven-minute interval. The same mean values are plotted in figure 1 as percentage change from the control values against time after the rebreathing began.

The mean curve of pulmonary ventilation reached its peak 4 minutes after rebreathing began. Respiration began to fail from 3½ to 6 minutes, and completely ceased from 4½ to 7½ minutes after asphyxia began. Alveolar CO_2 continued to rise throughout the experiments, from a control mean of 6.48 percent to 14.10 percent at death. Every animal showed a progressive rise in alveolar CO_2 content.

Though the arterial pressure was not regularly recorded, in all cases it dropped so low that no more blood could be withdrawn. The average critical period be-

tween cessation of respiration and failure of blood pressure to the point where no more blood could be drawn was 2.7 minutes.

A mean rise in whole blood CO_2 content from 41.5 to 57.1, or a change of 15.6 vol. percent, occurred during the first 8 minutes, followed by a fall to 52.1, at the end of 10 minutes. The decreasing CO_2 content was shown by 7 of the 10 dogs reported here. Mean blood oxygen fell from a control level of 18.03 vol. percent to 0.33 vol. percent, 69.4 percent of the oxygen being lost during the

TABLE 1. MEAN EXPERIMENTAL DATA ON ASPHYXIATED DOGS

Each figure is an average of data from 8 to 10 dogs, unless otherwise stated. The standard deviations are given below each figure.

	NORMAL	2 MIN.	4 MIN.	6 MIN.	7 MIN.	8 MIN.	9 MIN.	10 MIN.
Respiration analyses								
% CO_2 in alveolar air	6.48	8.44	10.07	11.83	13.80[1]	13.67[1]	14.17[2]	14.10[2]
σ	0.74	0.70	1.05	1.39	0.35	1.80	1.62	1.84
Alveolar pCO_2 in mm. Hg	48.0	59.3	70.7	83.5	90.3[2]	95.1[1]	97.8[1]	98.5[2]
σ	4.51	4.35	7.22	8.95	13.14	12.86	12.24	24.36
Pulmonary ventilation in cc/min.	1153	3618	5236	3596[1]	2892[2]			
σ	280	198	2432	2462	634			
Arterial blood analyses: whole blood as drawn								
Vol. % CO_2	41.51	46.35	50.78	53.59	51.80[2]	57.07[2]	51.0[2]	52.1[3]
σ	5.55	4.97	5.43	6.03	2.40	2.99	8.63	4.36
Vol. % O_2	18.03	13.04	5.54	1.92	0.37[2]	0.99[2]	0.44[3]	0.33[2]
σ	2.70	1.73	3.35	1.82	0.31	0.42	0.14	0.18
pH 37°	7.26	7.22	7.19	7.13	7.09[2]	7.07[2]	7.07[2]	7.00[2]
σ	0.04	0.06	0.05	0.05	0.06	0.09	0.07	0.05
Hematocrit	39.4	37.7	41.2	43.9	49.2[2]	48.3[2]	47.6[2]	50.5[3]
σ	6.6	8.1	4.6	7.2	2.2	2.2	6.1	3.8
Lactic acid content in mEq/L.	1.22	1.15	1.49	2.08[1]	2.92[2]	3.10[2]		3.40[2]
σ	0.58	0.45	0.47	0.85	0.80	1.28		1.85
Heart rate/min.	140	126	117	88	31[2]	94[2]	34[3]	
σ	30.3	35.5	30.9	41.1	17.0	45.3	10.3	

[1] 6 or 7 animals averaged. [2] Less than 6 animals averaged. [3] 2 animals averaged.

first four minutes of asphyxiation, and 89.4 percent within the first six minutes. A temperature correction of −0.01 pH unit per 1°C. rise was applied to the pH values measured at room temperature (9). The results indicate a steady fall in arterial pH from a control mean of 7.26 to a terminal value of 7.00.

Control hematocrit values spread from 30.8 to 52.1 percent. As asphyxia progressed, however, the percentage in each dog rose, resulting in a mean increase of 28.2 percent during 10 minutes of asphyxia.

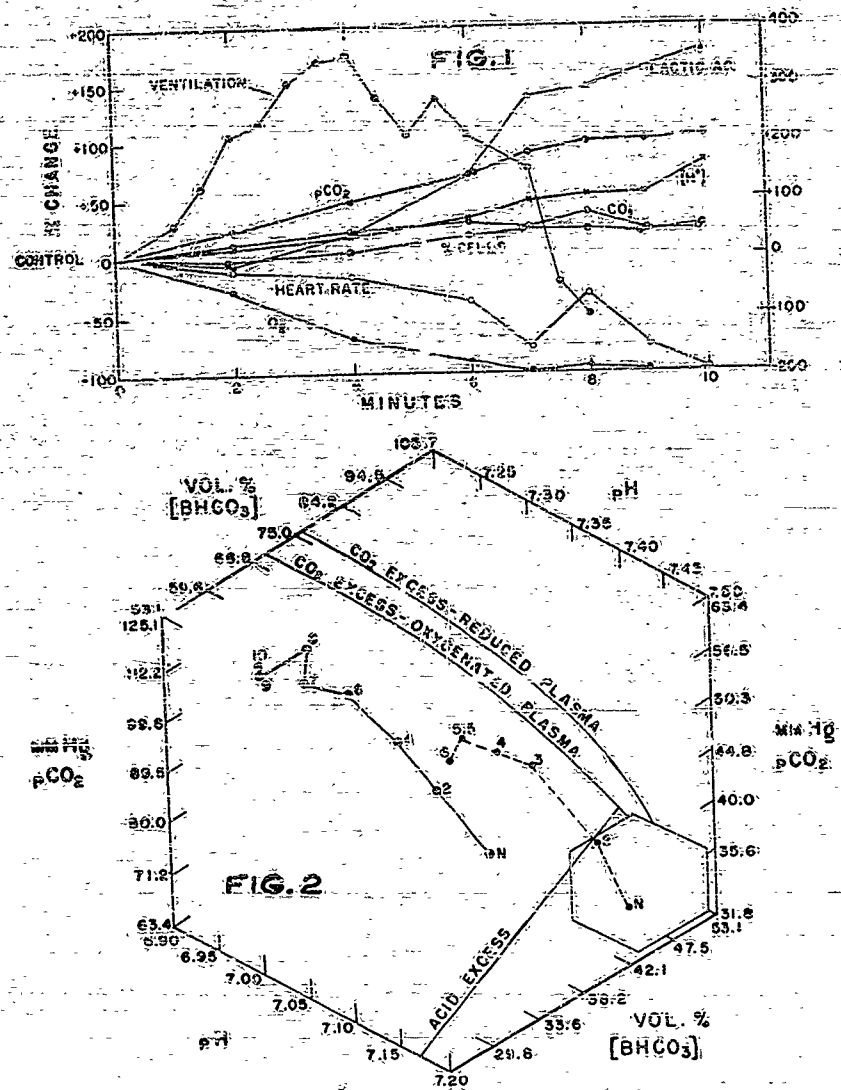

FIG. 1. SUMMARY OF VARIABLES OBSERVED DURING ASPHYXIA. The mean values of each variable are expressed as per cent change from the control. On the right is the scale for pulmonary ventilation. All other variables are plotted using the left-hand scale.

Ventilation = cc. pulmonary ventilation/minute; pCO_2 = alveolar tension in mm.Hg; Lactic ac. = mg. lactic acid/100 cc. whole blood; O_2 = cc. O_2/100 cc. whole blood; CO_2 = cc. CO_2/100 cc. whole blood; (H^+) = hydrogen ion concentration of plasma at 37° C.; % cells = hematocrit (4000 r.p.m. for 20 minutes); Heart rate = recorded by electrocardiogram.

FIG. 2. ACID-BASE BALANCE OF THE BLOOD DURING ASPHYXIA. The small interior hexagon represents the range of normal variation of dogs, as determined by Grodins, Lein, and Adler; this Journal 147: 433, 1946 (see text). The solid line represents the mean acid-base displacement of our dogs during asphyxia. (The calculations of the $(BHCO_3)$ value of the last (10 min.) point by the Van Slyke and Sendroy nomogram make use of only two hematocrit values, separated by 5.5 per cent. Calculations using individual hematocrit values of 46.0 and 51.5 per cent give values of 52.6 and 54.1 $(BHCO_3)$ respectively). The dashed line indicates the mean acid-base path of Grodins' asphyxiated dogs, reproduced from available data and graphs.

Lactic acid content of the arterial blood rose from a mean control level of 11 mgm. percent to 30.6 mgm. percent after 10 minutes of asphyxiation. The rise in lactic acid content did not become marked, however, until after about 6 minutes of asphyxiation, following which it rose very rapidly. This rise accompanied the fall of arterial oxygen below five volumes percent. This same relationship was pointed out by Scholander (10, 11) and Grinnell, Irving, and Scholander (12) on arrested breathing experiments with several species of animals.

The control heart rate, as recorded by the string galvanometer, was exceedingly variable from animal to animal, though the heart rate of each animal gradually decreased as asphyxia progressed. Cardiac change occurred, after respiration had ceased, usually in the form of auricular fibrillation and complete heart block.

TABLE 2. DOG MUSCLE CO_2 CONTENT—CONTROL AND DEATH FROM ASPHYXIA

EXPERIMENT NUMBER	MUSCLE ANALYZED	TOTAL CO_2 IN VOL. PERCENT		COMBINED CO_2 IN VOL. PERCENT		
		Normal	Death	Normal	Death	Av. Δ CO_2
8	Tibialis anterior	36.5	31.6	33.9	26.4	
		29.0	25.0	26.4	19.8	−7.0
	Peroneus longus	32.8	37.0	30.2	31.8	
		35.6	29.9	33.0	24.7	−3.3
9	Tibialis anterior	36.7	37.1	33.6	30.8	
		34.2	37.2	31.1	30.9	−1.5
	Peroneus longus	35.4	38.6	30.3	32.3	
		36.0	29.1	34.9	22.8	−5.0
10	Tibialis anterior	—	33.1	—	27.4	
		33.8	33.5	31.0	27.8	−3.2
	Peroneus longus	36.2	35.9	33.4	30.2	
		37.9	38.6	35.1	32.9	−2.7
Mean		34.9	33.9	32.1	28.2	
Average Δ CO_2						−3.8

A supraventricular tachycardia that cannot further be defined is the cause of the increase in mean heart rate at the eight-minute interval.

Complete muscle data are found in table 2. The mean difference between samples of the same muscle is 3.04 vol. percent, and the σ of the difference is 2.12. Total CO_2 was analyzed directly by the Danielson and Hastings technique. The combined CO_2 content was obtained by subtracting from the total CO_2 content the amount of CO_2 dissolved at the pCO_2 to which the muscle was subjected. This assumes a CO_2 absorption coefficient in muscle of 0.41, after Irving, Foster, and Ferguson (13). Muscle pCO_2 was estimated as arterial (alveolar) pCO_2 plus 6 mm. Hg (A-V difference), on the doubtful assumptions that the A V pCO_2 difference is a constant in spite of different circulation rates, and that muscle pCO_2 is the same as venous pCO_2.

DISCUSSION

Our experimental data concerning the acid-base balance of the blood, as expressed by the Henderson-Hasselbalch equation, $pH = pK_1 + \log \frac{(BHCO_3)}{(H_2CO_3)}$, have been plotted as a solid line on the logarithmic triaxial graph (fig. 2) introduced by Shock and Hastings (14). The inner hexagon represents the normal acid-base range of dog blood determined by Grodins *et al.* The pathways of CO_2 excess represent averages of *in vitro* CO_2 absorption curves of oxygenated and reduced true plasma (Shock and Hastings, 15; taken from the data of Henderson, 16). These pathways, as well as the fixed acid excess path, are in accordance with *in vivo* experimental observations of Shock and Hastings (15).

Our data are plotted from alveolar pCO_2, measured directly, and plasma ($BHCO_3$), calculated from whole blood ($BHCO_3$) by the Van Slyke and Sendroy (17) nomogram. This nomogram makes use of mean hematocrit values for each time interval. The mean figure for the last (10 min.) point is an average of only two hematocrit values, separated by 8.9 percent. Nomogram calculations making use of the individual hematocrits, 46.0 and 54.9 percent, give values of 52.6 and 54.4 vol. percent ($BHCO_3$), respectively.

It will be noted that the pH values so determined agree within 0.05 pH unit with experimental pH values corrected to 37°C., (with the exception of the mean figure for the nine-minute interval). A depression of the respiratory center, due to anesthesia alone, must account for the relatively acid pH and high pCO_2 of the 'normal' sample.

The acid-base displacement curve of our dogs agrees very closely with that of Grodins *et al.*, who asphyxiated dogs by completely obstructing the trachea, and whose results are shown approximately as a dashed line on figure 2.

Our data, with those of Grodins *et al.*, can best be described as representing an initial respiratory acidosis, associated with decreasing pH, increasing ($BHCO_3$), and increasing pCO_2. Superimposed on the respiratory acidosis toward the end of asphyxia is a slight uncompensated metabolic acidosis, characterized by a decreasing pH, decreasing ($BHCO_3$), and increasing pCO_2. The source of metabolic acidosis in these experiments appears to be an accumulation of lactic acid and other fixed acids from the anaerobic glycolysis taking place in the absence of oxygen, and displacing CO_2 from the blood. The accumulation of lactic acid in the blood is shown by the direct measurements of lactic acid content indicated in table 1.

Approximately 2 percent of the 28.2 percent rise in hematocrit can be accounted for by the shifting of water from plasma to cells, accompanying the acid-base changes of the blood during the experiment (16). The remaining 26.2 percent is explained by two possible mechanisms, neither of which was actually observed in these experiments, but both of which are known to occur in asphyxia: 1) discharge of red blood cells from the spleen into the circulation in response to lowered oxygen tension and 2) leakage of fluid and whole plasma into tissues, and a consequent hemoconcentration associated with shock. Thompson and

Birnbaum (2) have found regular evidence of shock in dogs subjected to obstructive asphyxia. Grodins *et al.* report an increase in hemoglobin content of 24.6 percent during obstructive asphyxia in dogs.

Inspection of table 3 reveals that the CO_2 content of the muscles is no higher at the end of asphyxia than at the beginning, as would be the case if these muscles stored the CO_2 displaced from the blood; rather, the mean death sample CO_2 content is 3.8 vol. percent lower than the control, despite increasing CO_2 tensions in the muscles. Each figure for muscle CO_2 content in table 3 is an average of four CO_2 analyses: two of tibialis anterior and two of peroneus longus. By comparison of our muscle CO_2 data with the CO_2 dissociation curve and muscle buffering power data found for dog muscle by Irving, Foster, and Ferguson, we have estimated the amount of fixed acid necessary to account for the decrease in muscle CO_2 content, despite increased muscle pCO_2, as asphyxia progressed. For this purpose it has been assumed, as previously, that muscle pCO_2 equals arterial (alveolar) pCO_2 plus 6 mm. Hg. Muscle pH is calculated from the Henderson-

TABLE 3. SUMMARY OF DOG MUSCLE EXPERIMENTS

EXPERIMENT NUMBER	COMBINED CO_2 IN MUSCLE	ARTERIAL pCO_2 plus 6 mm. Hg	MUSCLE pH	ESTIMATED LACTIC ACID CONTENT OF MUSCLE AT DEATH	LACTIC ACID CONTENT OF ARTERIAL BLOOD AT DEATH
	Vol %	*mm. Hg.*		*mEq/L.*	*mEq/L.*
8 Control	30.9	48.5	7.17		
Death	25.7	95.9	6.79	9.65	3.40
9 Control	32.5	56.6	7.12		
Death	29.2	116.0	6.80	8.68	5.24
10 Control	33.2	51.0	7.18		
Death	29.6	105.4	6.85	9.05	2.71

Hasselbalch equation, the pK_1 value being 6.1. Recent evidence of Conway and Fearon (18) for carbamino-bound CO_2 in muscle would make these pH values considerably lower, though the relative changes would be the same.

The estimated muscle lactic acid content at death (table 3, column 5) varies from 8.68 to 9.65 mEq./liter. Simultaneous lactic acid contents of the blood (table 3, column 6) range from 2.71 to 5.24 mEq./liter, or approximately one-third to three-fifths the muscle lactic acid values. This is evidence that arterial lactic acid, at the time the circulation ceases, has not come into equilibrium with muscle lactic acid, which is formed by anaerobic glycolysis, and diffuses outward into the circulation. These figures furnish a measure of the degree of metabolic acidosis existing in the tissues at the time of death from asphyxia.

At the time of respiratory failure from asphyxia in man, if the CO_2 concentration in the alveolar air is as high as it averaged in the dogs reported here—11 to 13 percent—CO_2 narcosis would be an important factor in respiratory failure. Blood CO_2 content would be so high that the respiratory center would presumably be depressed; vasodilatation and a fall in blood pressure would ensue (19).

It is therefore questionable, whether, under such circumstances, administration of carbogen would have the beneficial effect desired. Rather, it would seem that the additional CO_2 would serve to narcotize the respiratory center to an even greater degree. Until the CO_2 tension of the blood was reduced below the narcotic level, no beneficial effect could be derived from the added CO_2. Before the 'safe' level of CO_2 was attained in the blood, the critical period between cessation of respiration and heart change (about 30 seconds) would possibly have passed; efforts at resuscitation are of no avail a few seconds after the heart has stopped.

SUMMARY

1. Ten healthy anesthetized dogs were asphyxiated by rebreathing limited amounts of room air. A continuous pulmonary ventilation record was made, and electrocardiographic records, arterial blood, and alveolar air samples were taken simultaneously at one- or two-minute intervals during asphyxiation. Analysis of arterial CO_2, oxygen, and lactic acid content, pH, and hematocrit percentages were made. Alveolar samples were analyzed for CO_2 content. Control and death samples of muscle were analyzed for CO_2.

2. The acid-base balance of the blood responded to asphyxia with a respiratory acidosis, and a late metabolic acidosis superimposed. Direct measurements indicated that incoming lactic acid is the cause of CO_2 displacement from the blood during metabolic acidosis.

3. Muscle CO_2 content of dogs is slightly lower at the time of death from asphyxia than it is normally. This decrease in CO_2 content is a measure of the diffusion gradient of lactic acid from tissues to blood and of the degree of metabolic acidosis in the tissues during asphyxia.

4. The initial use of carbogen in resuscitating men subjected to any form of obstructive asphyxia is questioned.

The writer is deeply indebted to Professor Wallace O. Fenn and Dr. Arthur B. Otis for their counsel and constant encouragement throughout this research.

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ALVEOLAR CO_2 MEASURED BY EXPIRATION INTO THE RAPID INFRA-RED GAS ANALYZER

by

A. B. DuBois[1], R. C. Fowler[2], A. Soffer, and W. O. Fenn

This paper presents observations of carbon dioxide concentrations in the expired air analyzed by the Rapid Infra-Red Gas Analyzer designed and built in this laboratory by Dr. Richard C. Fowler (1). The apparatus gives a record of the carbon dioxide as percent of dry gas at each instant of expiration, with a response time of approximately .15 seconds. The normal expiratory curve is described, the effect of voluntary hyperventilation and exercise shown, and the result of expiring different volumes in equal times and equal volumes in different times is analyzed. Diffusion of alveolar CO_2 into the physiological dead space during breath holding is measured by using a pneumotachometer in conjunction with the analyzer. The continuous record of rebreathing different mixtures of carbon dioxide and air in a bag is depicted by interposing the analyzer between the mouth of the subject and the bag. The expiratory curves of a subject with advanced emphysema and pulmonary fibrosis are shown.

THE NORMAL EXPIRATORY CURVE

Rested subjects are seated at the breathing tube of the 'Rapid Infra-Red Gas Analyzer'. Two minutes are allowed for the subject to become accustomed to the slight added resistance and dead space and then several respiratory cycles are recorded. The analyzer is then calibrated with known carbon dioxide mixtures. A typical curve is shown in Fig. 1. The slopes of lines tangent to the mid regions of curves of four normal subjects are recorded in Table 1. The following events can be distinguished.

During inspiration room air passes through the analyzer. As expiration begins, the breathing tube is cleared of fresh air by the gas from the trachea, which is relatively unperfused by blood and therefore has a low output of carbon dioxide. This, in turn, is replaced by alveolar gas. Because the boundaries of these types of gas are mixed, each instant reveals different fractions of each type. The time necessary for the alveolar gas to travel up the trachea to the analyzer may be estimated as in the following example. If it were necessary for the alveolar gas to displace 200 cc. of 'dead air' ahead of it, and if the expiratory flow were 400 cc/second (24 Liters/min.), this delay would be 200/400 or 0.5 second. Because of forward and backward mixing, some of the alveolar gas would appear earlier and some later than the predicted time. However the rapid initial rise of the expiratory curve indicates that the spread of time about the mean for the initial alveolar sample is small, 93% of alveolarization being within plus and minus 0.2 second of the mean time in the resting curve of Fig. 1. The term 'mean alveolar carbon dioxide' must be explored to account for the gradual rise of CO_2 tension during the expiration of gas that is thought to come from the alveoli.

1 Work done during the tenure of a Life Insurance Medical Research Fellowship.
2 Supported in part by a John and Mary R. Markle Scholarship.

Figure 1

Curves of Resting, Exercise, and Hyperventilation obtained on the rapid infra-red gas analyzer show different slopes of CO_2 concentration in gas from the alveolar region. There are time interruptions at 0.2 second intervals.

TABLE 1

Normal Expiratory Slope, Expressed as cc CO_2 (STPD) Per Hundred cc of Dried Expired Gas Per Second

Subject	Slope
AD	.07
AS	.03
RS	.11
HB	.10
Mean	.09

EXPIRATION OF DIFFERENT VOLUMES IN EQUAL TIMES

The subject, breathing through the analyzer, is connected by means of a three way stop cock, at the end of a normal inspiration, to a recording spirometer and required to breath out at a given rate to a given depth by controlling his expiration so that the indicator on the spirometer follows an inclined line on the revolving kymograph drum. Different volumes of expiration may be achieved in equal times, and the effect on the CO_2 slope determined.

The result of such an experiment is shown in Fig. 2 where a pneumotachogram, to indicate the relative rates of flow, is seen as the fainter of the two lines. Measured slopes, volumes, and times are recorded in Table 2 for this and other subjects Many had to be repeated because of the inconstancy of the mean alveolar CO_2 over

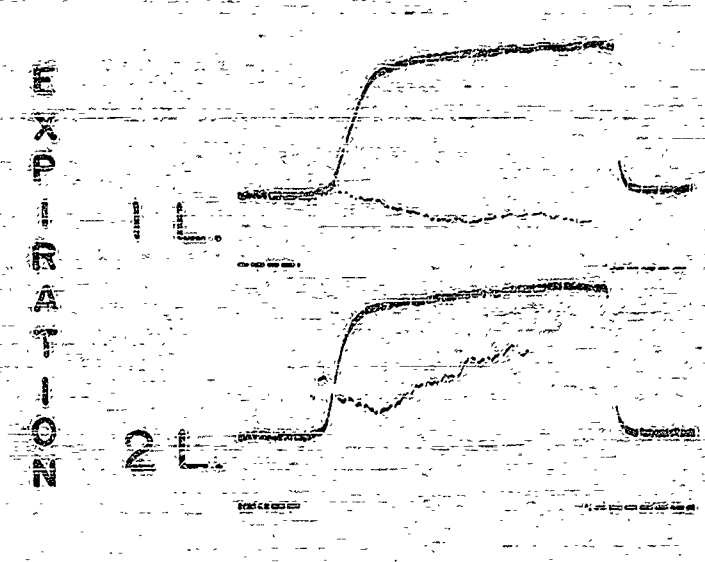

Figure 2

Expirations of different volumes in equal times, analyzed for CO_2 by the rapid infra-red gas analyzer, show similar rates of rise of CO_2 concentration in the gas leaving the alveoli. The pneumotachograph is the fainter line, and there are time interruptions at 0.2 second intervals.

TABLE 2

Rise of CO_2 Slope Over a Period of Four Seconds During Expirations of Different Volumes in Equal Times (5 sec.). The Change in CO_2 is Expressed as cc CO_2 (STPD) Per Hundred cc of Dried Expired Gas Per Four Seconds

	Volume expired, Liters (ATPS)			
Subject	1.00	1.50	2.00	2.58
AS	.7	.7	.7	.7
	.7	.5	.7	1.0
AD	.8	.4	.6	.8
	.7	.5	.6	.7
WD	.8	.9	.8	.8
	.5	1.0	.8	.8
JL	.9	.9	1.1	1.0
	.9	.7	.8	.8
HR	.9	1.0	1.1	.9
Mean	.77	.73	.80	.83

tive period of minutes. The conclusion from this experiment is that variation of the depth of expiration does not enable one to account for any appreciable portion of the normal expiratory slope of CO_2. The following experiment will be found to contribute much more to the explanation of the slope.

EXPIRATION OF EQUAL VOLUMES IN DIFFERENT TIMES

The subject expires through the analyzer into a spirometer in such a way as to cause the pointer of the spirometer to follow an inclined line on a revolving kymograph drum. In some cases he must pause for five seconds or ten seconds before starting his expiration. The rate of expiration is also varied, by varying the slope of the line on the kymograph drum. The result of breathing out rapidly, slowly, and after a pause is shown in Fig. 3. It is apparent that the path of the expiratory curve

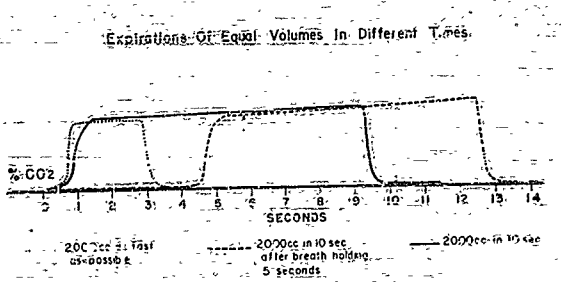

Figure 3

Tracings of three expirations of equal volumes in different times are superimposed to show that the CO_2 concentrations of gas from the alveoli rises with time rather than volume of expiration. A rapid expiration, prolonged expiration, and delayed expiration are shown.

of CO_2 is about the same in each instance. The concentration of CO_2 in the expired air seems to be dependent on the length of time that has elapsed between the end of inspiration and the moment when the gas leaves the alveoli (about half a second to one second before it reaches the analyzer window). The slope of the CO_2 in the expiration following breath holding up to 45 seconds duration is not increased. Thus the curves do not show evidence of 'stratification' of the gases with breath holding.

EXPIRATORY CURVES OF EXERCISE AND HYPERVENTILATION

The subject rides a stationary bicycle hard for two minutes, then sits and breathes through the rapid infra-red gas analyzer. Several expirations are recorded, a prolonged expiration being reproduced in Fig. 1. Another day, the rested subject hyperventilates in the sitting position for a minute, a recording of CO_2 then being made, Fig. 1. It will be noted that the expiratory slopes after exercise and during hyperventilation are steeper than for the resting subject breathing normally. If the hyperventilation is continued for half an hour, the slope again diminishes, but at a lower level. These findings conform to the principle that the slope is proportional to blood flow, which is increased by exercise, and arterio-venous P_{CO_2} difference, which is increased by hyperventilation (until restored by a lowering of venous tension).

DIFFUSION OF CO_2 INTO THE DEAD SPACE DURING BREATH HOLDING

To measure the physiological dead space, a flow meter consisting of a porous bronze disc and membrane manometer to record the pressure drop across the disc

is attached to the breathing tube of the rapid infra-red gas analyzer. Simultaneous recordings of flow and CO_2 in the expired gas are made. A line is drawn along the top of the expiratory curve of CO_2 and extrapolated backward over the portion of the curve representing various mixtures of alveolar CO_2 and dead air. The Bohr formula is applied to approximately each tenth of a second of expiration, using the extrapolated line as representative of alveolar CO_2 for each instant. The 'dead fractions of expired air' thus computed for each tenth of a second are added together to obtain the total physiological dead space. Individuals held their breath in the inspiratory position for varying lengths of time, and then expired into the apparatus. Figure 4 shows a normal expiration and an expiration following ten seconds of

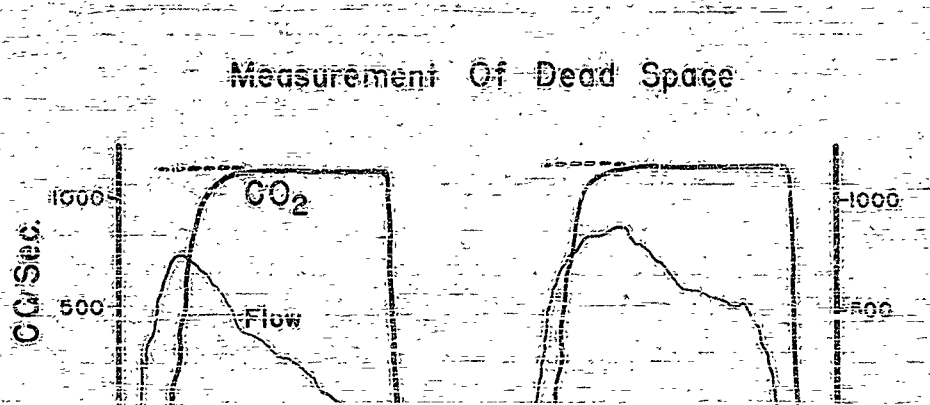

Figure 4

Tracings of the CO_2 curve and pneumotachogram as used in computing physiological dead space. The dead fraction of the expired gas for each tenth of a second is multiplied by the volume of the expired gas, and the dead volumes added to obtain the total dead space. The dashed line depicts the fact that the alveolar CO_2 slope is extrapolated backward for computing the dead fraction of gas. The dead space appears to diminish during breath holding, due to mixing of the alveolar gas with the dead space air.

breath holding, traced onto graph paper. It can be seen by inspection that the carbon dioxide rises earlier after the onset of expiration in the curve following breath holding. When the dead space represented by each tenth of an inch on the graph paper, converted to volume, and corrected for apparatus dead space and lag of the analyzer, is compared with and without breath holding one finds a definite and progressive diminution in dead space with breath holding. Thirty-eight curves were measured for dead space without breath holding. The range of values was 154-279 cc.,

with a mean of 177 cc. Twenty-seven curves were measured after intervals of breath holding ranging from 5 to 55 seconds. The ratio of dead space after breath holding to dead space without breath holding is recorded in Table 3. The variability of estimation of dead space on ten successive breaths from one subject is 11 cc., with a standard deviation of 8 cc. The correction for apparatus dead space was

TABLE 3

Effect of Breath Holding on Dead Space

	D.S.	D.S.(t) / D.S.(0)							
Subj.	(0)	(5)	(10)	(15)	(20)	(25)	(30)	(55)	Seconds of Breath Holding
A.S.	214	.7	.4	.2	.4	.3	.3	0	
A.D.	214	1.2	.6						
J.D.	156			1.0					
R.S.	143			.5					
H.B.	154			.9					
W.F.	200	.8	.9						
W.D.	165			.6	.6		.4		
Mean	177	.9	.6	.6	.5		.3		

a fixed value of 34 cc., but the correction for lag of the analyzer varied from 2 to 52 cc., depending on the rate of flow and the rate of rise of the CO_2 curve. For comparing curves before and after breath holding, an attempt was made to keep the rates of flow or the rates of rise of the CO_2 curves as similar as possible to minimize the apparatus error. The flow meter was calibrated with a 'Flow-rater' (rotameter type) guage, but did not hold its calibration precisely from day to day due to adsorption of water on the disc. The data shows that the dead space decreased to about half its initial value after twenty seconds of breath holding. This is of the same degree as found for nitrogen by W. S. Fowler (2).

The implication of this experiment is that during breath holding there is some mixing between the alveolar gas and the dead space air. This is probably due to mechanical agitation of the gases by the cardiac impulse, slow diffusion of gases into each other at the interface by random molecular motion, and a small amount of diffusion of CO_2 from the mucous membranes of the upper respiratory tract into the dead space (3). When alveolar CO_2 moves into the dead space an equal amount of dead space air must move into the alveolar space giving the effect of continued ventilation at the rate of about 90 cc in twenty seconds or 270 cc per minute. If the breath is held with the glottis open, there is influx of air due to the respiratory exchange ratio (R.Q.). The latter may give a ventilation of the order of 2/3 of the oxygen consumption, or about 180 cc per minute by the end of 20 seconds of breath holding. If these two effects are additive, the total alveolar ventilation may be as high as 450 cc per minute during the first twenty seconds of breath holding, though the effects may not be additive if the influx due to R.Q. effect sweeps back the alveolar gases that are being agitated into the dead space.

REBREATHING CO_2 TOWARD EQUILIBRIUM BETWEEN LUNG AND BAG

Inspiration of air containing CO_2 above venous P_{CO_2} will raise the P_{CO_2} of alveolar air with whatever blood and tissues are at arterial P_{CO_2} to a level close or equal to the mixed venous P_{CO_2} (oxygenated). In this state exchange will be equal between capillaries and alveolar air, so that the level of CO_2 should neither rise nor fall until recirculation takes place. Such an equilibrium would also presuppose that whatever tissues were going to exchange had done so; otherwise there would be a gradual downward drift of the P_{CO_2}.

The approach toward venous level is a logarithmic one, the rate being proportional to the distance from it at a given time. The asymptote is venous P_{CO_2} and the exponential constant is

$$\frac{(B-47)\ (\text{Blood Flow})\ (\text{Dissociation Constant for } CO_2)}{(\text{Volume of Bag and Equivalent Lung Volume for } CO_2)}$$

The term 'Equivalent Lung Volume for CO_2' includes the capacity of the alveolar air, capillary blood, and pulmonary tissue for carbon dioxide.

A subject is seated in front of the rapid infra-red gas analyzer, the breathing tube of which is connected to a rebreathing bag kept at BTPS in a thermostatically controlled box. The bag contains about two liters of a mixture of CO_2 and air, which the subject rebreathes for 15 to 20 seconds. Continuous rapid analysis gives a record of the concentration of CO_2 in the last normal expiration, the inspired mixture, and inspiratory and expiratory mixtures throughout the rebreathing period and on recovery. Eight different mixtures were rebreathed in sequence by subject AD. Three of the resulting records are traced, superimposed, to show that the curves approach a horizontal line and that there is no tendency to depart from this line even at twenty seconds (Fig. 5). When the CO_2 concentration in the inspired

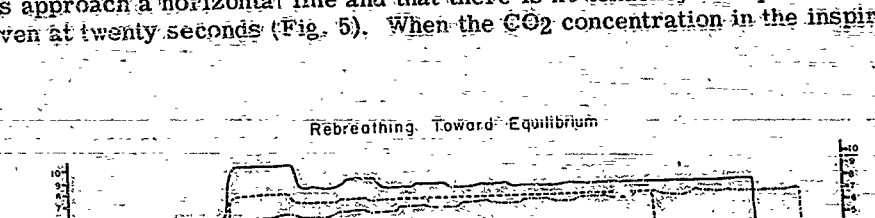

Figure 5

Rebreathing with the rapid infra-red gas analyzer interposed between the mouth of the subject and a 2 liter bag filled with 10% CO_2 (solid line), 7.5% CO_2 (dashed line), and 5% CO_2 (dot-dash line). Venous CO_2 tension is approached logarithmically from above or below, and maintained up to about twenty seconds when reached by breathing an intermediate mixture.

mixture is too high the concentration diminishes during rebreathing, but does not necessarily reach venous level. When the inspired CO_2 concentration is too low the

bag lags behind the alveolar air of the lung and the two approach but do not necessarily reach venous level. When the CO_2 in the inspired gas is just sufficient to raise the concentration of CO_2 in the lung to venous tension, the mixture in the lung and bag comes to an equilibrium where the concentration of CO_2 neither rises nor falls for a period of twenty seconds (for this particular subject). The procedure of rebreathing has been used by many investigators to obtain the venous tension of CO_2 (4). These curves are shown to illustrate the problem of mixing between lung and bag, the logarithmic approach toward the venous asymptote from above or below, and the use of the rapid analyzer in depicting the events that take place.

EMPHYSEMA

The subject in this experiment had such severe pulmonary emphysema that he was dyspneic in bed, and production of the record was difficult. He managed to give three maximum expirations separated by periods of ordinary breathing. From the portion of the record reproduced in Fig. 6 it may be seen that the expiratory reserve, though small in volume, was high in CO_2 concentration. The first air out

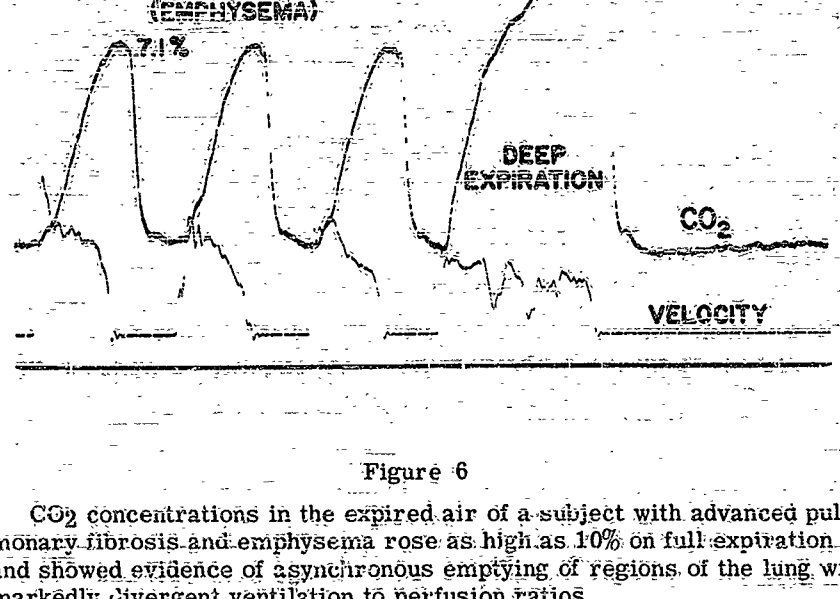

Figure 6

CO_2 concentrations in the expired air of a subject with advanced pulmonary fibrosis and emphysema rose as high as 10% on full expiration and showed evidence of asynchronous emptying of regions of the lung with markedly divergent ventilation to perfusion ratios.

was low in CO_2 because it must have come from areas with a low perfusion to ventilation ratio, and the last out from areas with a higher ratio and a high CO_2 content. The transcending slope is much greater than can be accounted for on the basis of the expected rate of rise of CO_2 concentration. The unperfused fraction of the tidal air can be approximated by the Bohr formula applied to the total expired air, but it

does not seem profitable to refine this further by computing the unperfused fraction of air for each instant of expiration because different regions of the lung emptying simultaneously may have markedly different perfusion to ventilation ratios. The mathematics would be further complicated by the fallacy of assuming the absence of a mean alveolar to arterial P_{CO_2} gradient in the face of a wide distribution of these ratios (5,6). Suffice it to say that in this subject there seems to be wide regional variation about the mean alveolar P_{CO_2} for any particular phase of respiration. This variation is presumably induced by regional inequalities in the perfusion to ventilation ratio, and appears in the curve because of asynchronous emptying of the various regions.

SUMMARY

1. The normal expiratory curve of CO_2 concentration shows a rapid rise as the mixed air is expired. After the dead space is cleared the slope assumes a gentle rise of approximately a tenth of a percent of CO_2 per second.

2. Expirations of different volumes in equal times, equal volumes in different times and after breath holding show a gradually rising slope of the same order of magnitude as the slope of the normal curve.

Expiration immediately following exercise shows an increase in the CO_2 slope, attributed to the increased rate of blood flow through the lungs.

4. Expiration during the early phases of hyperventilation shows an increase in the CO_2 slope, at a lower level of CO_2 concentration. The increased slope is attributed to increased arterio-venous tension difference of CO_2. The slope diminishes if hyperventilation is continued.

5. During breath holding there is an apparent mixing of alveolar CO_2 with the physiological dead space air. This is measured on the rapid analyzer.

6. Rebreathing of various mixtures of CO_2 yields curves that demonstrate the approach to a virtual venous tension of CO_2 that remains unchanged in subject AD for twenty seconds.

7. The expiratory curve of CO_2 in a subject with advanced emphysema shows an increase in CO_2 concentration with depth of expiration, reaching 10% CO_2 at the end of a deep expiration. This curve is interpreted as representing gas from regions of the lung with unequal ventilation -perfusion ratios and asynchronous emptying.

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ALVEOLAR CO_2 DURING THE RESPIRATORY CYCLE

by

A. B. DuBois[1], A. G. Britt, and W. O. Fenn

This paper presents data on the concentration of carbon dioxide in the alveolar air during the first twenty seconds of breath holding, and following inspirations of measured volume. The results are analyzed by application of the Fick principle and the relationship that "concentration of CO_2 equals the amount of CO_2 divided by the volume in which it is present." By application of these same principles the fluctuations of concentration and partial pressure of CO_2 in the alveolar gas are calculated throughout a respiratory cycle, and certain relationships between the mean alveolar CO_2 and the CO_2 in the expired gas are pointed out on the basis of this fluctuating curve. This curve is of use in determining the best method for delivering alveolar samples. It is also of use in interpreting the gradual rise in CO_2 concentration found by expiration into the Rapid Infra-Red Gas Analyzer of R. C. Fowler (1).

Fluctuations in alveolar CO_2 have been described by Benzinger and Konig (2), and calculated independently of the present authors by A. B. Chilton and R. W. Stacy (personal communication). It is hoped that this paper will supplement the data and the methods on which the calculations of others are based.

BREATH HOLDING CURVE

The subject is seated holding a Haldane tube whose sampling outlet delivers to a Cambridge Thermoconductivity CO_2 Analyzer, arranged for the analysis of single samples. At the onset of a normal expiration the subject presses a stop watch. At the end of this normal expiration he holds his breath for a predetermined number of seconds, at the end of which he empties his expiratory reserve rapidly and completely into the Haldane tube, stopping the watch, and turning the three way stop cock to trap the sample for analysis. About four samples each at minimum time, 5, 10, 15, and 20 seconds, in random order, are recorded. These are plotted, averaged, and a curve drawn to represent the change in concentration of alveolar CO_2 with breath holding. The average of six such curves on one subject is shown in Fig. 1. Total CO_2 output is measured by a five minute collection of expired gas in a spirometer whose volume, temperature, and CO_2 concentration are determined. Data on several subject is recorded in Table 1. One subject varied the procedure by rebreathing his tidal volume in a bag for comparison with the samples obtained by cessation of breathing. No difference was found in the type of curve produced. The subjects found that the Valsalva manoeuver diminished the alveolar CO_2 tension reached during a given interval of breath holding. Later measurements of oxygen tension during breath holding lead to the interpretation that the blood flow is probably slightly diminished during the early part of breath holding, recovering after a few seconds, and one would expect this to be exaggerated by the Valsalva procedure.

[1] This work was done during the tenure of a Life Insurance Medical Research Fellowship.

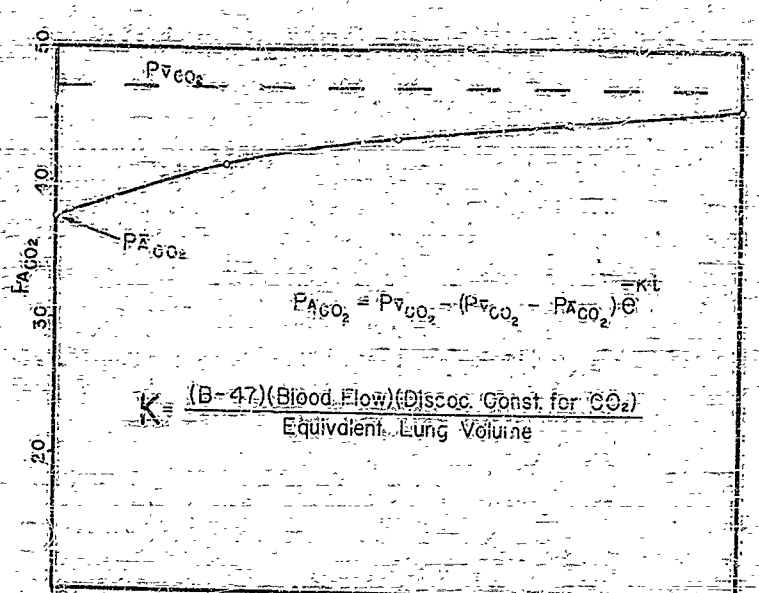


Figure 1

Breath holding curve of AD, average of 6 experiments. Alveolar $P\bar{C}O_2$ is seen to approach venous $P\bar{C}O_2$ (computed) as the asymptote of a logarithmic curve whose equation is shown on the figure. This applies to the first twenty seconds of breath holding.

It is necessary to draw a line through the points plotted on graph paper because a small amount of interpolation is necessary to obtain points that are equally spaced in 'time' for estimation of virtual venous CO_2 tension. This interpolation is done in the vicinity of the ten second point or by extrapolating the initial part of the curve back toward time 'zero'. The following derivation is used in finding a formula that can be used in interpreting the curves*. The symbols used are compatible with the 'Standardization of Definitions and Symbols in Respiratory Physiology' (17).

P_{ACO_2} Partial pressure of CO_2 in the alveolar gas at a given time.

$P\bar{A}CO_2$ Mean partial pressure of CO_2 in the mean alveolar gas.

$P\bar{v}CO_2$ Mean partial pressure of CO_2 in the mixed venous blood, oxygenated.

B Barometric pressure, expressed in mm. Hg.

V_{CO_2} Volume of CO_2

* This equation and method of interpreting the curve was presented at the Federation Meetings in Atlantic City March, 1950 (14), and at Copenhagen in August, 1950 (16).

TABLE I

Subj.	Minimum Time P_{CO_2}	Time	P_{CO_2}	Time	Seconds 10 P_{CO_2}	15 P_{CO_2}	20 P_{CO_2}	Mean CO_2 Output	Alv. Vol. BTPS	$P_{\bar{v}CO_2}$	ELV BTPS
AD	37.6	.6	39.5	4.0	42.4	43.6	44.5	295	3.9	45.8	5.60
AD	39.0	.8	42.2	4.5	45.0	46.7	47.5	317	3.9	48.9	4.56
AD	40.1	.6	42.6	5.3	43.7	45.0	45.2	296	3.9	46.1	7.61
+3L	29.1	1.2	31.2	5.3	33.9	35.1	36.8				
AD	37.0	.6	40.0	5.3	41.8	44.2	45.0	339	3.9	50.4	7.66
+3L	28.1	1.3	29.4	5.2	32.2	34.2	36.0				
AB	40.0	1.7	43.5	6.3	45.7	47.2	47.7	315	3.9	48.4	3.02
+3L	29.5	1.8	33.0	6.1	35.6	37.7	38.8				
WF	34.3	1.7	38.7	6.4	39.2	40.8	42.2	248	2.1	46.1	4.82
+3L	26.0	3.8			31.5		34.6				
WF*	36.4	1.8	38.6	5.0	41.2	43.2	44.7		2.3	46.9	4.79

* Rebreathing tidals

Data on Alveolar P_{CO_2}, Seconds of Breath Holding, Mean CO_2 output, and Alveolar Volume (Functional Residual Capacity minus the Dead Space). Venous P_{CO_2} (oxygenated) and Equivalent Lung Volume, ELV, for CO_2 are computed as in text. Lines designated '+3 L' represent breath holding curves at increased lung volume done on the same day as the curve at resting lung volume immediately above. Measured times are indicated at minimum time and 5 seconds of breath holding because of the critical nature of these points.

t — Time, a variable except when made specific by a subscript.

K — A constant whose meaning is specified when used.

Dissoc. Slope — The mean slope of the dissociation curve for CO_2 and whole blood, normally about .46 volumes percent per mm. Values given by Field et al (3) are used throughout this paper.

In a given time, the increase in CO_2 concentration in the lungs is the increase in amount of CO_2 divided by the volume into which this amount is delivered. The increase in amount of CO_2 is found by applying Fick's principle:

$$V_{CO_2} = (P\bar{v}CO_2 - P\bar{A}CO_2)\ (\text{Dissoc. Slope})\ (\text{Blood Flow})\ (\text{time})$$

Divided by the 'equivalent lung volume for CO_2' (a term that includes the capacity of the alveolar gas, pulmonary capillary blood and tissue for CO_2) and put into differential form this yields a change in partial pressure:

$$\text{I.}\quad dP_{ACO_2} = \frac{(P_{\bar{v}CO_2})\,(\text{Dissoc. Slope})\,(\text{Blood Flow})\,(\text{B-47})}{\text{Equivalent Lung Volume}}\,dt$$

By rearranging to $\dfrac{dP_{ACO_2}}{P_{\bar{v}CO_2} - P_{ACO_2}} = K\,dt$

where $K = \dfrac{(\text{Dissoc. Slope})\,(\text{Blood Flow})\,(\text{B-47})}{\text{Equivalent Lung Volume}}$

we can integrate to:

$$\text{II.}\quad P_{ACO_2} = P_{\bar{v}CO_2} - (P_{\bar{v}CO_2} - P_{\bar{A}CO_2})\,e^{-Kt}$$

Using two points of alveolar CO_2 and time of breath holding to solve for "K":

$$\text{III.}\quad K = \frac{\log_e \dfrac{P_{\bar{v}CO_2} - P_{ACO_2}(t_1)}{P_{\bar{v}CO_2} - P_{ACO_2}(t_2)}}{t_2 - t_1}$$

Using K to solve for the 'equivalent lung volume for CO_2':

$$\text{IV.}\quad \text{Equivalent Lung Volume} = \frac{(\text{Dissoc. Slope})(\text{Blood Flow})\,(\text{B-47})}{K}$$

where blood flow is expressed in hundreds of cc. per second. The blood flow is found by application of Fick's principle using the mean rate of CO_2 output in cc STPD per second obtained by a five minute collection and analysis of expired gas. Mean alveolar P_{CO_2} is taken to be equal to mean arterial P_{CO_2}, and this is taken as the P_{CO_2} found by expiration in minimum time.

Venous P_{CO_2} (oxygenated) is found from three points:

$(P_{ACO_2(1)}, t_1)$, $(P_{ACO_2(2)}, t_2)$, and $(P_{ACO_2(3)}, t_3)$.

Equation II is rearranged to:

$$\log_e \frac{(P_{\bar{v}CO_2} - P_{ACO_2(1)})}{(P_{\bar{v}CO_2} - P_{ACO_2(2)})} = \log_e \frac{(P_{\bar{v}CO_2} - P_{ACO_2(2)})}{(P_{\bar{v}CO_2} - P_{ACO_2(3)})}$$

In the special case where the second time interval is equal to the first time interval, or $t_3 - t_1 = 2(t_2 - t_1)$:

$$(P_{\bar{v}CO_2} - P_{ACO_2(1)})\,(P_{\bar{v}CO_2} - P_{ACO_2(3)}) = (P_{\bar{v}CO_2} - P_{ACO_2(2)})^2$$

and the solution for venous P_{CO_2} is that of a quadratic equation:

$$\text{V.}\quad P_{\bar{v}CO_2} = \frac{(P_{ACO_2(2)})^2 - (P_{ACO_2(1)})\,(P_{ACO_2(3)})}{2(P_{ACO_2(2)}) - (P_{ACO_2(1)} + P_{ACO_2(3)})}$$

In practice, if one takes the first point as origin, and expresses the second and third points as increments, then the height of venous P_{CO_2} above the first point is found by squaring the increment of CO_2 of the second point and dividing this by the

difference of twice the increment of the second point and one times the increment of the third point (above the first). For example, the average of six curves on A.D. was plotted, a line drawn through the points, and values read from this curve as 37.5 mm Hg. at time O (by extrapolation), 43.3 mm at 10 seconds, and 45.6 mm at 20 seconds. Expressed as increments these points are 0, 5.8, and 8.1.

Then $P\bar{v}CO_2 - 37.5 = \frac{(5.8)^2}{2(5.8)-(8.1)} = 9.6$ mm. Then $P\bar{v}CO_2$ is 47.1 mm Hg.

To compute the CO_2 output from the onset of breath holding to any particular time of breath holding, within twenty seconds, one can consider that the amount that would have come out at the mean rate of CO_2 output would be represented on the graph of P_ACO_2 versus time as a rectangle bounded by a vertical line from the mean alveolar P_ACO_2 to the virtual venous tension, and a horizontal line from the mean alveolar P_ACO_2 along the time axis to the time in question. The remaining sides of the rectangle are formed to complete the figure. The area within this rectangle represents the amount of CO_2 that would have come out within that time if the breath had not been held; and the area within the rectangle and between the breath holding curve and the line representing virtual venous P_ACO_2 is, by comparison, the amount of CO_2 delivered by the flowing blood during breath holding (assuming constant blood flow).

The results of these computations are entered in Table 1. The 'equivalent lung volume' is found at STPD because it is necessary to use mean CO_2 output expressed at STPD, together with the dissociation constant for CO_2 which yields a figure for CO_2 in cc, STPD. This is also consistent with the use of B-47, because the fraction of CO_2 in dry air thus obtained had to be expressed as alveolar P_ACO_2. The equivalent lung volume is converted to BTPS for tabulation. The residual volume was measured by the nitrogen dilution method. The expiratory reserve volume was measured with a spirometer and converted from ATPS to BTPS. These are added to obtain the functional residual capacity, from which the dead space volume, arbitrarily taken as 165 cc BTPS, is subtracted to obtain the volume of the alveolar air BTPS. It will be noted that the 'equivalent lung volume' is usually greater than the volume of alveolar air. This discrepancy is attributed partly to alterations in pulmonary blood flow during breath holding, partly to concentration of gases due to the diminished R.Q. during breath holding, partly to diffusion of alveolar carbon dioxide into the dead space, and partly to a fraction of the CO_2 being taken up by the lung tissue, tissue fluid, and pulmonary capillary blood.

The conclusion drawn from the breath holding curves is that the CO_2 concentration in the lungs rises with time despite relative constancy of lung volume and depth of expiration. The rate of rise is proportional to the arterio-venous P_ACO_2 difference and blood flow, and inversely proportional to the size of the reservoir into which the CO_2 is delivered by the blood.

INSPIRATION OF A MEASURED VOLUME

The alveolar P_ACO_2 that results from inspiration of a known volume of air is measured by having the subject come to the end of a normal expiration, turn a three way stop cock to connect his mouth to a spirometer containing three liters of air

(ATTS), inspire rapidly until the spirometer is empty, turn the three way stop cock to connect his mouth to a Haldane tube, expire fully as rapidly as possible, and turn the three way cock to trap the sample for analysis by the Cambridge CO_2 analyzer. A pneumotachograph is used to measure the elapsed time of the procedure. Duration of inspiration is 1 to 3 seconds, duration of expiration is listed in Table 1. The subject obtains points for a breath holding curve at increased lung volume by pausing at the end of his inspiration from the spirometer. Points thus obtained are tabulated for comparison with the breath holding curve done at resting lung volume, and are marked '+3 L.' in the Subject column.

Although the lung volume is nearly doubled, the alveolar P_{CO_2} is not diminished to half its initial value as one might expect from simple dilution. The rise in alveolar P_{CO_2} that one can attribute to the blood perfusing the lungs during the time of inspiration and expiration is indicated, to some extent, by the initial slope of the breath holding curve at increased lung volume, and is not sufficient to explain the failure of inspiration to lower the alveolar P_{CO_2} more than it does. The two factors that probably contribute toward this 'damping' phenomenon are increased rate of blood flow during inspiration, and CO_2 coming out of the pulmonary capillary blood and tissues. These two factors work in the same direction to yield an 'equivalent lung volume for CO_2' that is greater than the lung air volume, and about the same for inspiration as for breath holding.

A sample calculation of the equivalent lung volume for CO_2 from data in the table is as follows: Subject AD, at the end of a normal expiration, had an alveolar CO_2 tension similar to that of the minimum time Haldane sample, 40.5 mm Hg. This was present in a volume of gas consisting of 1.6 L BTPS residual volume, .2 L BTPS dead space, 2.2 L BTPS expiratory reserve volume, totaling 4.0 L BTPS functional residual capacity. The volume of CO_2 present, at barometric pressure 748 mm Hg., was $\frac{(4.0)(40.5)}{(701)} = 232$ cc BTPD. The alveolar CO_2 tension at the end of inspiration, found by extrapolating the breath holding curve at increased lung volume back 1.3 seconds to time 'zero', was 28.3 mm Hg. This was present in a volume of gas consisting of 1.6 L BTPS residual volume, 2.2 L BTPS expiratory reserve volume, and 3.2 L BTPS volume of inspired air, totaling 7.0 L BTPS alveolar volume. The volume of CO_2 present was $\frac{(7.0)(28.3)}{(701)} = 283$ cc BTPD. The CO_2 coming into the alveolar gas during inspiration was then 283-232 cc BTPD or 44 cc STPD. The duration of inspiration was 1.5 seconds, the blood flow approximately 173 cc/sec, the mean arterio-venous tension difference during inspiration $46.9 = \frac{40.5+28.3}{2}$ or 12.5 mm Hg., the slope of the CO_2 dissociation curve .48, and hence the amount of CO_2 yielded at the mean rate of blood flow 16 cc STPD. The CO_2 unaccounted for is then 44-16 or 28 cc during a change of CO_2 tension of 40.5-28.3 or 12.2 mm. The CO_2 in excess is thus 2.3 cc STPD per mm Hg., enough to give a change in tension of 12.2 mm in a volume 2.3 x B-47 or 2.3 x 701 = 1.6 L gas. The equivalent lung volume for CO_2 at the onset of inspiration was then 1.6 L BTPS residual volume, 2.2 L BTPS expiratory reserve volume, and 1.6 L BTPS in excess, totaling 5.4 L BTPS.

For further discussion of the effect of ventilation on pulmonary blood flow it is suggested that the reader consult Armitage and Arnott (4), and Lauson, Bloomfield and Cournand (5). The possibility of variation in the composition of mixed venous blood is mentioned by Forssander and White (6) with Dr. H. C. Bazett. Some of the interpretation of the data presumes the absence of an arterial-alveolar membrane gradient, as shown by Suskind et al (7). The alteration of the respiratory exchange ratio (R.Q.) during expiration is described by Stacy and Kydd (8) and during breath holding by Ferris (10) and Otis, Rahn and Fenn (9). Diffusion of CO_2 into the dead space has been measured in this laboratory (11) and diffusion of nitrogen into the dead space by W. S. Fowler (12). Equilibration of alveolar gases with pulmonary capillary blood has been discussed by Kety (13), and with reference to breath holding by DuBois, Soffer, Fowler and Fenn (14). More recently a detailed mathematical analysis of diffusion of CO_2 from the capillary to the alveolar space has been made by Chilton and Stacy of Ohio State University (personal communication). Uptake of CO_2 by pulmonary tissue has been mentioned by Richards and Strauss (15) and estimated by Fenn and DuBois (16). Data on dogs lungs equilibrated with various tensions of CO_2 and analyzed for CO_2 content (unpublished) indicates that this tissue factor is not negligible.

ALVEOLAR CO_2 CONCENTRATION DURING EXPIRATION

The expiratory curves found by rapid analysis of the expired gas for CO_2 are unlike the breath holding curve described above in that they do not have the concave downward logarithmic form characteristic of the latter. To account for this observation, the effect of diminishing lung volume must be entered into the equation for the breath holding curve. This is done by substituting a variable lung volume for the constant 'equivalent lung volume' in the differential expression for rate of change of CO_2 concentration as a function of arterio-venous tension difference. Since a prolonged expiration may be at a constant rate of flow $\dot{V}_E$ starting with an initial equivalent lung volume $ELV_{(O)}$ the equivalent lung volume at time 't' will be:

$$ELV_{(t)} = ELV(O) - \dot{V}_E t$$

Replacing the constant ELV in equation I by this linear function of time:

$$\frac{dP_{ACO_2}}{dt} = \frac{(P_{\bar{v}CO_2} - P_{ACO_2})\,(\text{Dissoc. Const})\,(\text{Blood Flow})}{ELV_{(O)} - \dot{V}_E t} \quad \text{(B-47)}$$

Rearranging:

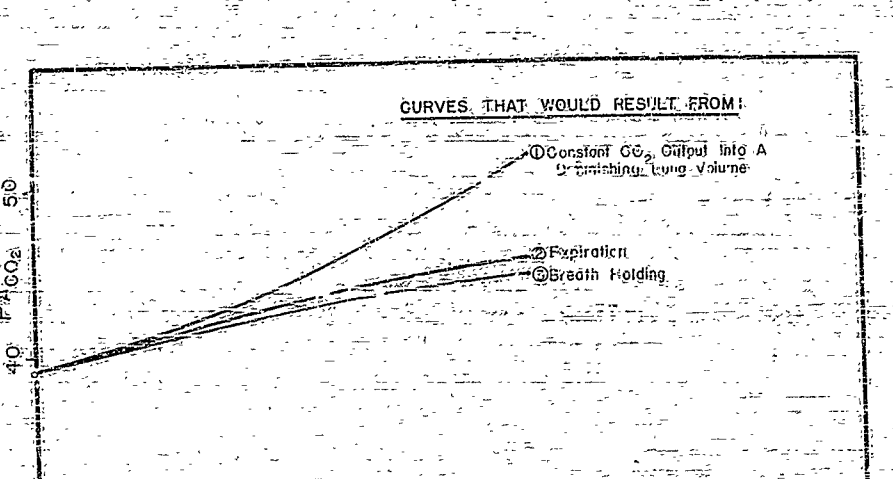
$$\frac{dP_{ACO_2}}{P_{\bar{v}CO_2} - P_{ACO_2}} = \frac{(\text{Dissoc. Const.})\,(\text{Blood Flow})\,dt}{ELV_{(O)} - \dot{V}_E t} \quad \text{(B-47)}$$

Integrating both sides:

$$\text{VI.} \quad \text{Log}_e\,(P_{\bar{v}CO_2} - P_{ACO_2}) = \frac{(\text{Blood Flow})(\text{Dissoc Const.})\,(\log_e(ELV_O - \dot{V}_E))}{\dot{V}_E} + C$$

where C is a constant of integration*. The effect of diminishing lung volume on a breath holding curve is depicted in Fig. 2.

* This equation presented at the Federation meetings March, 1950.



Expiration Causes The Alveolar P_{CO_2} To Rise More Rapidly Than Breath Holding Because The Lung Volume Diminishes

Figure 2

The expiratory curve of CO_2 (center) computed from equation VI is a compromise between the exponential tendency due to diminishing lung volume (top) and the logarithmic tendency of the breath holding curve computed from equation V.

COMPUTATION OF ALVEOLAR CO_2 DURING INSPIRATION AND EXPIRATION

Just where the mean alveolar P_{CO_2} may be expected to occur during an expiration is of particular interest when it is necessary to compare the expiratory curves obtained by rapid analysis or Haldane type samples to equations that use the 'ideal alveolar CO_2' which has been found useful in the 'steady state' (alveolar air equation, and Ventilation-Perfusion ratio of Rahn and Riley). To picture this mean it will be useful to plot the alveolar CO_2 concentration at all phases of the respiratory cycle from information about the CO_2 output per minute, blood flow, mean arterio-venous P_{CO_2} difference, equivalent lung volume for carbon dioxide obtained from the breath holding curves, and a pneumotachograph adjusted to the appropriate tidal volume by assuming a dead space of 160 cc and applying a formula relating alveolar ventilation to blood flow. The computation is done by stepwise application of Fick's principle and the relationship: Concentration of CO_2 equals amount of CO_2 divided by equivalent lung volume. The concentration is computed for each tenth of a second during a cycle, each tenth yielding information necessary for computation during the next tenth second. Details of the computation may be found in the appendix.

The conditions chosen are representative of a subject seated in a laboratory and undergoing active testing, but without exercise. They are as follows:

Barometric Pressure (Rochester, N.Y.)	747 mm Hg.
Mean arterio-venous P_{CO_2} difference	9.8 mm Hg. oxygenated.
Mean blood-flow through lungs	7.00 L/min.
Frequency of respiration	15.0 cycles/min.
Mid-expiratory P_{CO_2}	39.20 mm Hg.
Dead air space	.160 Liters
Slope of the dissociation curve for CO_2 from the mean arterial to the mean venous point (oxygenated)	.46 cc CO_2/mm/centum (STPD)
Equivalent lung volume for CO_2, at end of normal expiration	6.0 Liters BTPS

Substituting this information into the Fick equation one finds that the CO_2 output is 316 cc STPD per minute. Using the ventilation equation one finds an alveolar ventilation of 6.99 liters BTPS per minute, or tidal volume of .626 liters BTPS per breath.

The fluctuations in alveolar CO_2 during the breathing cycle, computed by the method described and using the assumptions listed above, are depicted in Fig. 3. The saw toothed curve has the following characteristics:

A. With the onset of inspiration tracheal air is drawn back into the alveoli, permitting continuation of the expiratory rise in CO_2 concentration, though with slope diminished by the increasing lung volume.

B. The maximum is reached when the rate of dilution of alveolar CO_2 by fresh air exactly counterbalances the ratio of CO_2 output to equivalent lung volume.

C. The CO_2 concentration drops rapidly as the effect of dilution exceeds that of CO_2 output.

D. The minimum is reached near the end of inspiration when the ratio of 'CO_2 output to equivalent lung volume', which is augmented by the increased arterio-venous difference, exceeds the 'dilution-per-unit-volume by air', which is diminished by the decreasing rate of flow.

E. With the onset of expiration the upward slope is continued, being slightly concave downward as venous P_{CO_2} is approached, but diverted above the logarithmic curve of breath holding by virtue of diminishing lung volume.

It will be seen by inspection of this curve that the mean alveolar CO_2 tension lies slightly above mid-expiratory P_{CO_2}. However the mean P_{CO_2} in the alveolar fraction of the expired gas is slightly less than mid-expiratory P_{CO_2} because the major volume of gas comes out early in expiration. Although the P_{CO_2} of the arterial blood is determined by the former mean, the fraction of CO_2 in the expired gas is determined by latter. This discrepancy will affect the calculation of dead space by the Bohr formula and the use of the ventilation equation in conjunction with the Fick principle.

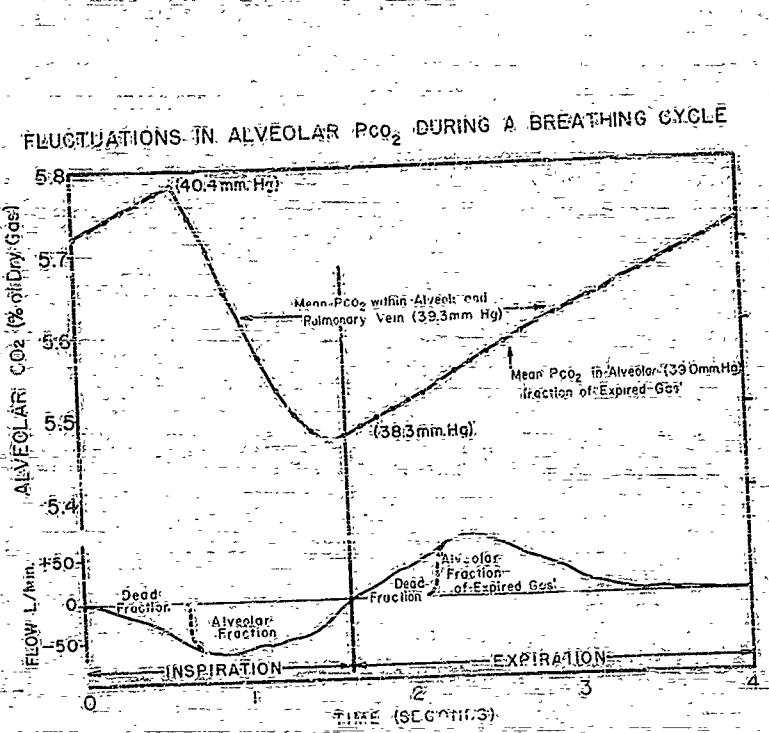


Figure 3

Fluctuations in alveolar PCO_2 computed for a normal respiratory cycle. There is a damping effect due to variation of blood flow, and capacity of tissue for CO_2. The best time for an expired sample of mean alveolar gas for CO_2 determination is shortly after midexpiration. If most of the alveolar gas expired comes out early in expiration, the CO_2 therein will have a lower tension than that of the mean arterial blood.

APPENDIX

Method for computing Alveolar PCO_2 during the Respiratory Cycle

1. Assume a mean arterio-venous PCO_2 difference.

2. Assume a mean arterial PCO_2, and assume that this will be encountered at midexpiration time.

3. Assume a constant rate of perfusion with blood.

4. Assume a dead air space volume BTPS.

5. Assume a respiratory frequency.

6. Compute the CO_2 output/minute from the Fick Principle.

7. Estimate the difference in tension between the mean alveolar air and the alveolar fraction of expired air (due to assymetry of the expiratory flow curve).

8. Subtract this correction from the mean alveolar P_{ECO_2} to obtain the mean P_{CO_2} in the alveolar fraction of the expired air.

9. Use the ventilation equation to obtain the alveolar ventilation, BTPS.

10. Divide by respiratory frequency to obtain alveolar tidal.

11. Add Dead Space to obtain total tidal volume.

12. Assume an 'equivalent lung volume for CO_2' at the end of a normal expiration.

13. From a respiratory flow or spirometer tracing, proportionately redistribute the volume to correspond to the tidal and frequency of respiration assumed in this problem.

14. Add the redistributed tidal to the resting equivalent lung volume for CO_2 to obtain the equivalent lung volume for each tenth of a second during the cycle.

15. Construct a table with the following headings:

Time – From the onset of inspiration, in .1 sec intervals.

Equivalent lung volume – At each corresponding tenth sec.

P_{ACO_2} – Exists in the alveolar air at corresponding time.

$P_{\bar{v}CO_2}$-P_{ACO_2} – Arterio-venous difference at that time.

New CO_2 – Volume BTPS delivered by blood in .1 sec., using the Fick principle for that tenth second.

Tracheal CO_2 – Volume of CO_2 BTPS inspired from dead air space during the ensuing tenth second.

Total CO_2 BTPS – Volume of CO_2 that will be present by the end of the tenth second interval under consideration. This heading concerns inspiration.

$\Delta\%CO_2$ – $\frac{\text{New } CO_2 \times 100}{\text{Eq. L. Vol.}}$ This heading concerns expiration, and replaces the above heading for calculating the next heading listed.

New % CO_2 (dry) = Obtained by $\frac{\text{Total } CO_2 \text{ BTPS}}{\text{Eq. L. Vol BTPS}} \times 100$ during the inspiratory part of the cycle, and by subtracting $\Delta\%CO_2$ from the New $\%CO_2$ of the preceeding tenth of a second for the expiratory part. This New $\%CO_2$ refers to the end of the tenth of a second interval of the line on which it is tabulated, or the tenth second listed on the next line. Hence the division is made with the Eq. L. Vol. that exists at the time represented by the latter (on the next line). The P_{ACO_2} for this next line is calculated by multiplying the New $\%CO_2$ by $\frac{\text{B-47}}{100}$.

Use of the table for computing alveolar P_{CO_2} during the respiratory cycle: The computation must be started somewhere in the cycle. The most convenient time seems to be midexpiration. The values are entered in each column line after line to

TABLE 2

Table for Computing Alveolar CO_2 During Respiratory Cycle

Time	ELV	PCO_2	(A-V)%CO_2	NewCO_2	Tracheal CO_2	(BTPS) Total CO_2	(DRY) New%CO_2
0	6000	40.1	9.9	.59	.74	344.78	5.73
0.1	6013	40.1	9.8	.58	.40	345.76	5.74
0.2	6020	40.2	9.8	.58	.92	347.26	5.75
0.3	6036	40.2	9.7	.58	1.44	349.28	5.76
0.4	6061	40.3	9.7	.58	2.25	352.11	5.77
0.5	6100	40.3	9.7	.58	2.88	355.57	5.78
0.6	6150	40.4	9.6	.57	.58	356.72	5.74
0.7	6207	40.2	9.8	.58	.00	357.30	5.70
0.8	6269	39.9	9.1	.60		357.90	5.65
0.9	6334	39.5	9.5	.63		358.53	5.61
1.0	6369	39.3	9.7	.64		359.17	5.57
1.1	6450	38.9	10.1	.67		359.84	5.53
1.2	6504	38.7	10.3	.68		360.52	5.50
1.3	6552	38.5	10.5	.70		361.22	5.48
1.4	6591	38.3	10.7	.71		361.93	5.47
1.5	6616	38.3	10.7	.71		362.64	5.4730
1.6	6626	38.3	10.7	.71	$\Delta\%CO_2$	.0107	5.4637
1.7	6618	38.3	10.7	.71		.0107	5.4744
1.8	6598	38.4	10.6	.70		.0107	5.5051
1.9	6573	38.5	10.5	.70		.0107	5.5158
2.0	6537	38.6	10.4	.69		.0106	5.5264
2.1	6480	38.7	10.3	.68		.0106	5.5370
2.2	6414	38.7	10.3	.68		.0107	5.5477
2.3	6346	38.8	10.2	.68		.0108	5.5585
2.4	6275	38.9	10.1	.67		.0108	5.5693
2.5	6208	39.0	10.0	.66		.0107	5.5800
2.6	6151	39.1	9.9	.65		.0107	5.5907
2.7	6106	39.1	9.9	.65		.0108	5.6000
2.8	6069	39.2	9.8	.65		.0107	5.6107
2.9	6040	39.3	9.7	.64		.0106	5.6213
3.0	6018	39.4	9.6	.64		.0106	5.6319
3.1	6008	39.4	9.6	.64		.0106	5.6425
3.2	6001	39.5	9.5	.63		.0105	5.6530
3.3	5997	39.6	9.4	.62		.0104	5.6634
3.4	5996	39.6	9.4	.62		.0103	5.6737
3.5	6000	39.7	9.3	.62		.0103	5.6840
3.6	6000	39.8	9.2	.61		.0102	5.6942
3.7	6000	39.8	9.2	.61		.0101	5.7043
3.8	6000	39.9	9.1	.60		.0100	5.7143
3.9	6000	40.0	9.0	.60		.0099	5.7242
4.0	6000	40.1				343.45	

the end of expiration. The percent of CO_2 present at the end of expiration is converted to volume of CO_2 present (actually an 'equivalent volume of CO_2') by multiplying the percent by the equivalent lung volume on the next line. This total CO_2 is entered at the bottom of the table. To it is added the tracheal CO_2 and new CO_2 brought by the blood in the next tenth of a second, and this new total of CO_2 is entered in the appropriate column at the top of the table. On completing the cycle both ends should be found to meet exactly. If they do not, it is desirable to check the calculations in the table, the ventilation equation, and the apparent A-A gradient due to asymmetry of the flow curve. The gradient thus produced occurs during inspiration as well as expiration. It will be found that the mean alveolar CO_2 is greater than midexpiratory CO_2 and that the mean arterio-venous difference and the mean CO_2 output were therefore overestimated when one applied the Fick principle to the assumed bloodflow and A-V difference. This makes it necessary to alter the mean CO_2 output by about 1%.

SUMMARY

1. Alveolar P_{CO_2} plotted against time for the first twenty seconds of breath holding follows a logarithmic curve whose asymptote is virtual venous P_{CO_2} and whose negative exponential constant equals the slope of the dissociation curve of CO_2 times the rate of pulmonary blood flow times B-47 divided by the 'equivalent lung volume'. The latter is greater than the volume of alveolar air by virtue of the capacity of capillary blood of the lungs, pulmonary tissue, and tissue fluid for CO_2.

2. Factors that may disturb this curve are: alteration of the rate of pulmonary blood flow, recirculation, diffusion of alveolar gases into the dead space and vice versa, inhomogeneity of the alveolar air, and diminution of the lung volume due to the respiratory exchange ratio.

3. Expiration causes the P_{CO_2} in the alveolar air to increase more rapidly than one finds for breath holding. This is due to diminishing lung volume.

4. Fluctuations in alveolar CO_2 are computed for a normal respiration using the Fick principle and the relationship 'concentration equals amount divided by volume' for each tenth of a second of the cycle. Mean arterial CO_2 is shown to be theoretically slightly greater than the mean CO_2 in the alveolar fraction of the expired air by virtue of the asymmetry of the inspiratory and expiratory flow curves. Mean alveolar CO_2 can be sampled shortly after the middle of the expiratory period.

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ALVEOLAR CO_2 AND O_2 DURING BREATH HOLDING, EXPIRATION, AND INSPIRATION[1]

by

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The purpose of this paper is to obtain, from a detailed study of the changes in oxygen and carbon dioxide concentrations in alveolar samples during breath holding and inspiration, some estimate of the capacity of the pulmonary tissue and capillary blood for carbon dioxide. Although the method is devious, and the result approximate, the attempt has led the writers to see some physiological relationships that they had not recognized before.

The particular relationship in question is between carbon dioxide and oxygen during breath holding, inspiration, and expiration. When these gases are plotted as partial pressures on the diagram whose abscissa (X axis) is P_{O_2} and whose ordinate (Y axis) is P_{CO_2}, the composition of 'mean' or 'ideal' alveolar gas appears as a single point whose coordinates are approximately (100, 40). It has been pointed out by Rahn (1), and Riley and Cournand (2) that it is unlikely that gas of this exact composition exists in any particular alveolus because of regional inequalities of ventilation and bloodflow, but that it is improbable that variation from this point is of great degree in normal subjects because it would result in desaturation of the arterial blood. Those authors have further described the variation as being along a line passing through the mean alveolar point and determined by the respiratory exchange ratios between the blood and gas of the alveoli concerned. Ventilation and bloodflow both play a part in the respiratory exchange ratio.

It was found by Rahn and Otis (3) that varying the ventilation or bloodflow of the subject, but still maintaining both processes, resulted in the mean composition of the 'alveolar portion of the expired gas' travelling along the line which had been computed for variations in the composition of the gas within individual alveoli. However it was further noted that complete cessation of ventilation, as while holding the breath, resulted in an unsteady state in which the alveolar gas composition lay on a line that diverged from the line found when both ventilation and bloodflow were maintained. It will be shown in this paper that the breath holding pathway represents the 'bloodflow' component, and the pathway of rapid inspiration represents the 'ventilation' component, and that these two components are never in true equilibrium but rather in a cyclical balance as the subject breathes.

The cyclical variation in the composition of alveolar gas presents a problem to the physiologist who is interested in obtaining a sample of 'mean alveolar gas'. He must pick the right time in the cycle. In addition to distribution according to ventilation and bloodflow, the CO_2 and O_2 concentrations have a distribution according

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to 'time' or 'phase' of the respiratory cycle". Fortunately the variation is not large, as will be shown by calculation of oxygen and carbon dioxide during a normal cycle. However before proceeding to an analysis of the cycle, we shall describe the experimental method and analysis of data of breath holding and inspiration

EXPERIMENTAL METHOD

The seated subject is allowed to come into a steady state during the course of approximately half an hour. This condition is judged by relative constancy of alveolar samples delivered into a Haldane tube from the end of normal inspirations. The single samples are analyzed by a Cambridge thermoconductivity apparatus, for carbon dioxide, and a Pauling oximeter, for oxygen. Alveolar samples are then obtained about every two minutes as follows: The subject indicates by turning a three way breathing stop-cock on the Haldane tube that he has started a normal expiration. He holds his breath at the end of this normal expiration until told by the operator to 'blow'. He expells his expiratory reserve volume as rapidly as possible into the tube, and turns the stop-cock to trap the sample. Timing is done by the operator, who starts a clock at the onset of the normal expiration, as judged by turning of the stop-cock, and stops the clock at the end of the expiratory reserve sample, as judged by returning of the stop-cock. Expiration in minimum time is accomplished by having the subject breath out as rapidly as possible from the end of a normal inspiration. The operator has the subject deliver four to six samples each at minimum time, 5, 10, 15, and 20 seconds of breath holding, in random order. Total CO_2 output and O_2 consumption are then measured by collection of gas expired during five minutes through inspiratory and expiratory valves into a Tissot spirometer flushed with expired gas. The temperature, barometric pressure, volume, and gas concentrations in the spirometer are determined. Inspiratory points are then determined by having the subject deliver a maximum expiration, breathe in two liters of room air as rapidly as possible from a spirometer, and blow out as rapidly as possible into a Haldane tube for analysis by the Cambridge and Pauling apparatus. The expiratory reserve volume of the subject is measured with a spirometer, and the residual volume determined by the nitrogen dilution method.

Ten subjects were tested by the same procedure, except that one of them was tested on two occasions, and another did not have a five minute collection of gas for determination of minute volume. The expired gas of this subject was, however, analyzed for composition, making available the respiratory exchange ratio.

Data is presented in Table 1. The data was analyzed by expressing the change in alveolar P_{O_2} and P_{CO_2} (corrected for change in nitrogen fraction) as increments above the initial, minimum time, value. These increments were averaged according to time groups and analyzed as a 'mean curve', yielding the figures used in the example of calculation, and data for the graph of the mean P_{O_2}, P_{CO_2} curve (Fig. 1). They were also analyzed for each subject, using parallelograms to reduce the P_{CO_2}, P_{O_2} curve of each subject to the best fit to a logarithmic curve (see below). The asymptotes and exponential constants thus derived were averaged to see how they would compare with the constants derived from the 'mean curve.' They are tabulated with the data in Table 1. A better idea of the random scatter can be deduced from the latter approach than from the former, although it can be said of the mean curve that it gives a good fit of all five points to a mathematically drawn logarithmic curve.

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TABLE 1

Individual Breath Holding Values

Subject							B	(STPD) Mean CO_2 Output	(STPD) Mean O_2 Consumption	(STPD) Functional Res. Cap.	R_E	$R_{A(t1)}$	$P_{\bar{V}CO_2}$	$\frac{VA}{ELV}$
R.S.	Seconds	1.6	5.3	10.1	14.9	20.2	747.5	246	278	3.27	.882	.845	48.6	.67
	P_{ACO_2}	40.7	43.8	45.1	46.9	48.2								
	P_{AO_2}	99.7	97.5	92.6	87.1	82.5								
T.M.	Seconds	1.8	6.3	10.3	15.8	21.0	751	244	298	4.51	.820	.815	44.3	.84
	P_{ACO_2}	38.4	40.6	42.6	43.7	44.8								
	P_{AO_2}	101.8	99.4	94.2	89.6	87.6								
M.S.	Seconds	2.0	5.4	10.8	15.3	20.4	745	134	176	2.34	.776	.801	44.6	.51
	P_{ACO_2}	39.9	41.2	42.7	43.9	44.0								
	P_{AC_2}	98.2	96.6	91.9	86.5	84.3								
W.F.	Seconds	2.2	5.5	10.3	15.2	20.4	737	180	252	1.96	.746	.700	40.3	.98
	P_{ACO_2}	34.0	36.8	38.7	40.2	40.8								
	P_{AO_2}	98.7	95.0	89.0	83.3	78.0								
K.W.	Seconds	0.7	5.3	10.3	14.8	19.9	731	281	332	1.67	.857	.853	44.4	.88
	P_{ACO_2}	33.1	40.3	43.5	45.7	45.8								
	P_{AO_2}	105.3	91.3	84.3	68.0	64.5								
M.G.	Seconds	1.6	5.5	10.6	14.9	19.9	746	130	213	2.46	.847	.806	43.8	1.39
	P_{ACO_2}	38.9	41.0	42.1	43.9	44.4								
	P_{AO_2}	99.8	97.9	95.6	88.1	87.2								
R.F.	Seconds	1.4	5.8	9.9	14.9	20.1	751	194	259	2.71	.751	.753	43.5	.62
	P_{ACO_2}	38.0	39.3	40.6	42.1	43.4								
	P_{AO_2}	99.3	97.1	92.9	88.7	84.2								
H.R.	Seconds	1.5	5.3	10.1	14.8	19.8	751	228	253	3.31	.896	.907	44.9	.90
	P_{ACO_2}	38.0	41.1	42.1	43.2	44.7								
	P_{AO_2}	106.0	101.4	99.4	95.9	89.5								
A.D.	Seconds	1.1	5.2	9.8	15.6	19.4	750	267	305	3.35	.904	.825	45.9	.96
	P_{ACO_2}	39.2	42.2	43.9	45.0	46.1								
	P_{AO_2}	101.4	98.1	96.3	90.2	85.6								
A.D.	Seconds	1.1	5.0	10.0	15.0	20.0	750	217	277	3.35	.793	.837	44.9	.97
	P_{ACO_2}	37.2	40.5	42.8	44.3	45.5								
	P_{AO_2}	104.3	99.0	92.2	88.2	81.7								
E.G.	Seconds	1.3	5.4	10.5	15.0	20.1	752			2.04	.801	.787	$\frac{45.4}{44.6}$	$\frac{.46}{.83}$ SD .25
	P_{ACO_2}	39.7	40.6	42.2	43.7	44.7						Mean:		SE .08
	P_{AO_2}	99.1	98.0	92.0	86.3	80.2								

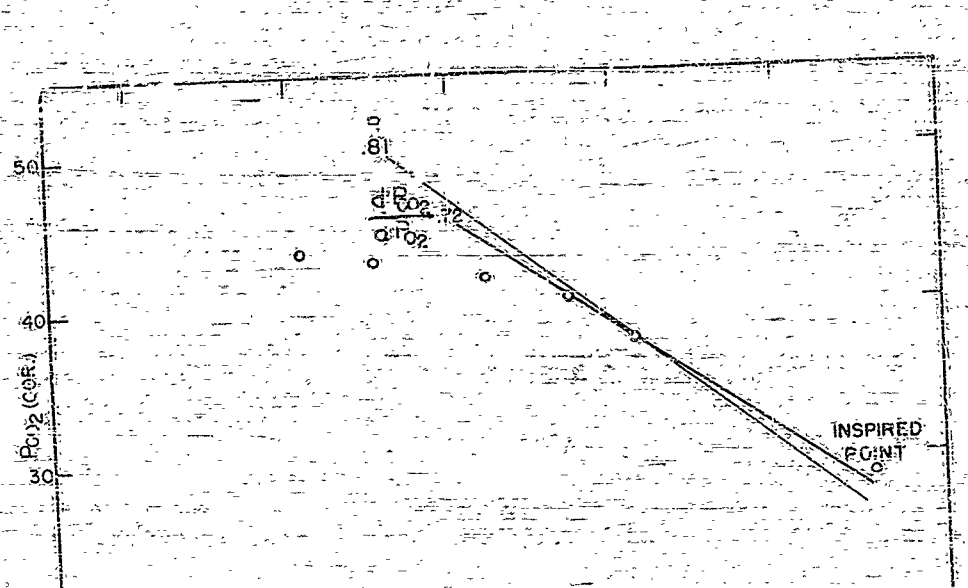

Figure 1

This is the mean breath holding curve of 11 experiments. The first point is similar to an 'end-inspiratory' Haldane sample, and lies practically on the line representing the mean respiratory exchange ratio of the expired gas ($\bar{R}$). The initial slope of this curve is approximately (.89) ($\bar{R}$) = .72. This curve has been corrected according to change in the nitrogen fraction during breath holding.

INTERPRETATION OF DATA

The method of interpreting the data hinges upon the principle that the rate of CO_2 output is proportional to the arterio-venous content difference, and that the concentration of CO_2 in the lung at any given time is equal to the amount of CO_2 divided by the volume in which it is distributed. The latter is termed 'equivalent lung volume for CO_2' to include the capacity of lung tissue and blood, as well as gas for carbon dioxide. A mathematical derivation based on the above assumptions results in an expression relating P_{CO_2} in the alveolar gas and time of breath holding from zero to twenty seconds as follows (4):

$$P_{\bar{A}}CO_2 = P_{\bar{v}}CO_2 - (P_{\bar{v}}CO_2 - P_{\bar{A}}CO_2)\, e^{-Kt}$$

$$K = \frac{(\text{Blood Flow})(\text{Dissoc. Const.}^*)}{(\text{Equivalent Lung Volume for } CO_2)} \quad \text{(B-47)}$$

* Mean slope of dissociation curve for CO_2 from arterial to venous level, oxygenated

where:

P_{ACO_2} is the alveolar CO_2 tension at a given time, t.

P_{vCO_2} is the partial pressure of CO_2 in the mixed venous blood, oxygenated.

P_{ACO_2} is the partial pressure of CO_2 in the mean alveolar air, assumed equal to that in mixed arterial blood.

e is the base of natural logarithms.

B is the barometric pressure in mm Hg.

Since P_{O_2} in the alveolar air during breath holding is approximately a linear function of time, we can substitute it for time in the relationship between P_{CO_2} and time of breath holding and derive a curve that will be similar to the latter curve but with a different exponential constant. Most of the variables that affect the breath holding curve of CO_2, such as bloodflow and lung volume, also affect the breath holding line of oxygen in such a way that when the P_{CO_2} is plotted as a function of P_{O_2} the undesirable variables cancel out and leave a logarithmic curve that is disturbed by a few minor errors that should be opposed to each other. First of these is recirculation of the blood. However recirculation of venous blood at diminished oxygen tension is partly counterbalanced by incipient and increasing desaturation of the arterialized blood at the end of breath holding. Increase in nitrogen fraction due to the absorption of oxygen being greater than the replacement with carbon dioxide gives an error in the curve of about a millimeter of CO_2 after twenty seconds of breath holding. This error should be corrected as far as calculation of the increment in volume of CO_2 is concerned, but not for purposes of estimation of P_{CO_2} in calculating the virtual venous P_{CO_2}. This dilemma is of small degree, and the authors have been inclined to make the correction on alveolar P_{CO_2} for change in nitrogen fraction on the basis that it will tend to counteract increase of P_{CO_2} due to recirculation. The P_{O_2} is also corrected according to change in nitrogen fraction. When this correction is made on the data, it is not necessary to correct the slope of the R.Q. line beyond the mean alveolar point on the oxygen - carbon dioxide diagram. The term 'alveolar P_{CO_2}' refers to the gas tension in the alveolar gas uncorrected for change in nitrogen fraction, and the same is true for oxygen. Data is listed this way, but computed values are based on the corrected data.

An alternative approach toward visualizing the changes in gas concentration is to consider the alveolar pathway on the P_{O_2} - P_{CO_2} diagram (Fig. 2). The alveolar point at any given time is the origin of a vector whose inclination represents the direction of travel and whose length represents rate of travel on the diagram. This vector is the resultant of a vertical component for P_{CO_2} and a horizontal component for P_{O_2}. The start of breath holding is at a point close to the intersection of the 'mean R.Q. line for blood,' as described by Rahn and Riley (1,2), and the vector is the resultant of the P_{CO_2} vector (upward), which is the mean rate of carbon dioxide output divided by the equivalent lung volume, and the P_{O_2} vector (horizontal), which is the mean rate of oxygen consumption divided by the volume of alveolar air (functional residual capacity minus the dead space). The slope of the resultant vector is the ratio of the former vector to the latter, and this in turn is the mean R.Q. times the ratio between alveolar volume and equivalent lung volume. The length of the CO_2 vector at time 't' is proportional to the anterio-venous gradient at time 't'

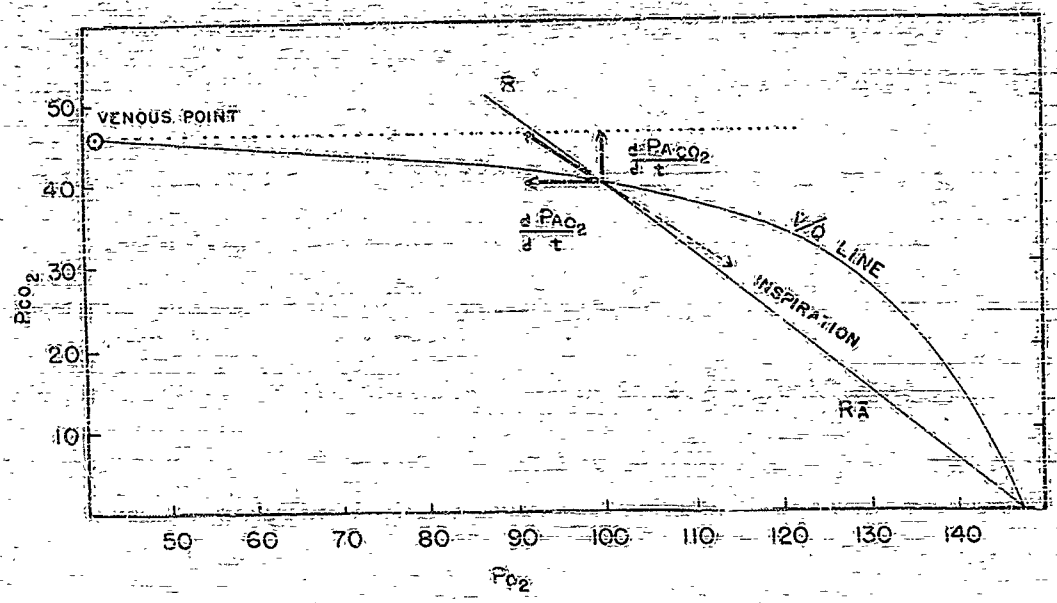

Figure 2

Vectors are used to illustrate the direction and rate of departure of the alveolar gas point, during breath holding and rapid inspiration, from the ventilation-bloodflow line and line of the mean respiratory exchange ratio (R). The dashed line is venous P_{CO_2}, oxygenated (although this should have another set of ordinates, it is placed on the chart for diagrammatic purposes).

whereas the length of the oxygen vector remains essentially constant because the arterio-venous content difference for oxygen does not change appreciably over the range under scrutiny.

MATHEMATICAL DERIVATION

The expression for $P_{\bar{A}CO_2}$ as a function of time is:

$$P_{\bar{A}CO_2} = P_{\bar{v}CO_2} - (P_{\bar{v}CO_2} - P_{\bar{A}CO_2})\, e^{-Kt} \qquad \text{(I)}$$

$$\text{where } K = \frac{\text{(B-47) (Bloodflow) (Dissoc. Const. for } CO_2\text{)}}{\text{(Equivalent Lung Volume for } CO_2\text{)}} \qquad \text{(II)}$$

The expression for $P_{\bar{A}O_2}$ as a function of time is:

$$P_{\bar{A}O_2} = P_{\bar{A}O_2} - \frac{\text{(Mean rate of } O_2 \text{ consumption) (B-47) (Time)}}{\text{(Alveolar volume)}} \qquad \text{(III)}$$

The latter is substituted into the former by a series of intermediate steps as follows:

$$\text{Mean } CO_2 \text{ output} = (\text{Bloodflow})(\text{Dissoc. Const.})(P\bar{v}CO_2 - P\bar{A}CO_2)$$

$$(\text{Bloodflow})(\text{Dissoc. Const.}) = \frac{\text{Mean } CO_2 \text{ output}}{P\bar{v}CO_2 - P\bar{A}CO_2} \qquad \text{(IV)}$$

Substituting (IV) in (II):

$$K = \frac{(B\text{-}47)(\text{Mean } CO_2 \text{ output})}{(P\bar{v}CO_2 - P\bar{A}CO_2)(ELV)} \qquad \text{(V)}$$

But CO_2 output = $(\bar{R})$ (Mean O_2 consumption)

Substituting this in (V):

$$K = \frac{(B\text{-}47)(\bar{R})(\text{Mean } O_2 \text{ consumption})}{(P\bar{v}CO_2 - P\bar{A}CO_2)(ELV)} \qquad \text{(VI)}$$

$$\text{But mean } O_2 \text{ consumption} = \frac{(dP_{AO_2})(V_A)}{(dt)(B\text{-}47)}$$

Substituting this in (VI):

$$K = \frac{(B\text{-}47)(\bar{R})(V_A)(dP_{AO_2})}{(P\bar{v}CO_2 - P\bar{A}CO_2)(B\text{-}47)(ELV)(dt)} \qquad \text{(VII)}$$

$$\text{But: } \frac{dP_{AO_2}}{dt} = \frac{P\bar{A}O_2 - P_{AO_2}(t)}{t}$$

Substituting this in (VI):

$$K = \frac{(\bar{R})(V_A)(P\bar{A}O_2 - P_{AO_2}(t))}{(P\bar{v}CO_2 - P\bar{A}CO_2)(ELV)(t)}$$

Substituting this in (I)

$$P_{ACO_2} = P\bar{v}CO_2 - (P\bar{v}CO_2 - P\bar{A}CO_2)e^{-(\bar{R})\left(\frac{V_A}{ELV}\right)\left(\frac{P\bar{A}O_2 - P_{AO_2}(t)}{P\bar{v}CO_2 - P\bar{A}CO_2}\right)}$$

This is the equation for the breath holding curve on the P_{O_2}, P_{CO_2} diagram, and is characterized by having an initial slope $\bar{R}\left(\frac{V_A}{ELV}\right)$, where V_A is alveolar volume and ELV is the equivalent lung volume for CO_2; it approaches venous P_{CO_2}, oxygenated, as the asymptote of a logarithmic curve. Other symbols that are used in the derivation are:

P_{AO_2} Partial pressure of oxygen in the alveolar gas at time t.

$P\bar{A}O_2$ Mean partial pressure of oxygen in the mean alveolar gas.

$\bar{R}$ Mean respiratory exchange ratio for carbon dioxide and oxygen (respiratory quotient).

d Symbol denoting 'partial derivative', or 'very small change in value'.

Venous P_{CO_2}, oxygenated, can be found from this curve by the same method used for finding it from the curve of alveolar P_{CO_2} versus time (4). However one must remember to use P_{CO_2} values at equal intervals of P_{O_2} rather than equal intervals of time. This may necessitate considerable interpolation in a curve plotted from single samples. The alternative of substituting points separated by unequal

P_{O2} interva ... the formula leads to a difficult solutio... ... expression:

$$\left(\frac{k}{k - x_2}\right) \quad = \quad \left(\frac{k \cdot \; x_2}{k - x_3}\right)^{t_2}$$

where 'k' re... ents $P_{\bar{v}CO2} - x_1$, t_1 is taken as zero time, and ... the P_{ACO2} at time 't'. Wh... equals $2t_2$, the expansion is of the quadratic form ... easily solved for '... otherwise the expansion becomes a series that is ... easily solved.

An ai... computing the asymptote has been devised and used on ... e data, co... rected for hi... fraction, presented in Table 1. Two parallelograms are constructed from ... board and brass rods (Fig. 3). On the wallboard side ... are scales representin... rements of P_{CO2} on one parallelogram, P_{O2} on the other. Threads

Figure 3

Parallel... grams used to obtain best fit of five experimental points to a mathematically d... wn logarithmic curve whose asymptote is known. The asym... ptote and exponential ... onstant of the experimental curve are determined from the degree of compressio... of each axis necessary to obtain the best fit of intersection of corresponding ... airs of vertical and horizontal threads to the mathematical curve. This is ess... tially simultaneous compression of the vertical and horizo... tal axes.

parallel to ... ... points along the sides, representing P_{CO2} on one set of boards, ... Corresponding ... threads are made to intersect at right ang... a previously drawn logarithmic curve ...

vertical axis controlling venous P_{CO_2}, and of the horizontal axis controlling the exponential constant. The best fit of the five points is obtained by varying the slant of the parallelograms, thus controlling the degree of compression of each axis. The threads are held taught by elastic bands along the sides of the wall boards, and kept on the points by pins placed in the scales according to the increase in gas tension. The degree of compression of the vertical axis can be estimated from the distance between two of the horizontal threads, and the arterio-venous tension difference of the original curve computed from the mathematically drawn logarithmic curve and its asymptote.

A hypothetical instrument for doing the same thing electronically would be an oscilloscope with a CO_2 meter attached to the Y-axis input and an O_2 meter attached to the X-axis input. The gain of each axis could be adjusted until the expiratory curve fell along a logarithmic line drawn on the face of the 'scope. From the degree of gain one could deduce the relationship between the original curve and the mathematical curve.

The exponential constant may be found in a way analagous to that used for the P_{CO_2} versus time curve (4). It equals the natural logarithm of the ratio between the arterio-venous P_{CO_2} differences for any two points, divided by the change in oxygen tension between the two points. This constant multiplied by the mean arterio-venous CO_2 tension difference is equal to the initial slope of the breath-holding curve, which is in turn equal to the mean respiratory exchange ratio (R) multiplied by the ratio of the alveolar volume to the equivalent lung volume. Thus:

$$\frac{V_A}{ELV} = \frac{(\text{exponential constant})(\bar{P}_vCO_2 - \bar{P}_ACO_2)}{R}$$

Knowledge of the mean arterio-venous P_{CO_2} difference is of importance in determining the initial slope of the breath holding curve, but not in determining the venous asymptote or the exponential constant of the curve. The mean arterial point is elusive in view of the respiratory fluctuations, and about the best one can do is to take the mean of several 'end-inspiratory' Haldane samples, that is an expiration delivered as rapidly as possible into a Haldane tube from the end of a normal inspiration. If one begins to deliver the sample at the end of a normal expiration, the P_{CO_2} will have risen too high (1). In practice, 'end-inspiratory' samples delivered in minimum time lie close to the mean R.Q. line determined by analysis of expired gas collected over a period of five minutes on each subject. The mean distance is .010 R.Q. units below the R.Q. line, with a standard deviation of .034 and standard error of the mean of .010 R.Q. units. The mean alveolar point is theoretically located near the mid-expiratory point in the diagram of respiratory fluctuations in alveolar P_{CO_2}. It is not necessary to know the arterio-venous content difference of oxygen, although this could be computed indirectly from the data.

To use a specific example of calculation, with data from the mean breath holding curve, the mean P_{CO_2} and P_{O_2} at 5, 10, 15, and 20 seconds of breath holding (corrected for increase in the nitrogen fraction) were expressed as increments above the minimum time points, and set up on the parallelograms. The points were found to give a good fit to the mathematical logarithmic curve when the vertical distance between two threads had been changed from 4.14 mm Hg. to 6.5 cm units.

The mathematical asymptote was 10 cm. units above the starting point, so the $\bar{P}CO_2$ asymptote must have been $10 \times \frac{5.14}{6.3}$ or 8.6 mm Hg. above its starting point. The exponential constant is found by taking the arterio-venous $\bar{P}CO_2$ difference, 8.6 mm, for the first point, and 2.46 mm for the third point, and the change in P_{O_2}, 9.11 mm between these two points, and using these as follows:

$$k = \frac{\log_e \frac{8.6}{2.46}}{9.11} = .109$$

Now: $(\bar{R})\ \frac{(\bar{V}_A)}{(\bar{\Sigma}LV)} = (.109)\ (8.6)$, and $\bar{R}$ is .81

Then: $\frac{(\bar{V}_A)}{(\bar{\Sigma}LV)} = \frac{(.109)\ (8.6)}{(.81)} = .89$

This is to say that when the breath-holding curve and mean R.Q. line are plotted on the P_{O_2}-P_{CO_2} diagram the curve starts out with a slope that is slightly less than that of the mean R.Q. line (no longer corrected for nitrogen fraction) by virtue of the fact that the CO_2 has to diffuse into the capillary blood and tissues of the lungs as well as into the alveolar air, thus giving the appearance of it having to go into a larger volume than the oxygen, which is relatively insoluble in the tissues and saturated blood, does. It will be seen from the above analysis of the situation that changes in blood flow, lung volume, diffusion into the dead space, and small amounts of recirculation will affect the rate of travel along the alveolar pathway of breath holding, but not the course, or direction of travel at any instant.

A study is made of the P_{O_2} versus time of breath holding for each subject. It is expected that the rate of change in P_{O_2}, corrected for nitrogen fraction, is proportional to the mean rate of oxygen consumption and inversely proportional to the alveolar volume of the subject. To put this into terms of an equation:

$$\text{delta } P_{A_{O_2}} \left(\frac{F_{N_2}(O)}{F_{N_2}(t)}\right) = \frac{(\bar{V}O_2)\ (\bar{B}\text{-}47)}{(\bar{V}_A)\ (60)} \text{ delta } t$$

On this basis the expected line for P_{O_2} versus time is drawn for each subject, and the observed points plotted for comparison. For purposes of comparison of the ten experiments, a mean rate of oxygen consumption for the group is found, and the points of P_{O_2} for each subject reduced to comparable values by multiplying the change in oxygen tension (corrected for nitrogen fraction) by the ratio of the mean oxygen consumption to the subject's oxygen consumption, the subject's alveolar volume to the mean alveolar volume, and the mean B-47 to the subject's B-47, thus:

$$\Delta P_{O_2} \text{ for comparison} = (\Delta P_{O_2} \text{ of subject}) \times \frac{(\bar{V}O_2)\ (\bar{B}\text{-}47)\ (\bar{V}_A)}{(V_{O_2})\ (B\text{-}47)\ (V_A)}$$

where the line over the symbol refers to the mean of the group. Variation about the mean expected line for oxygen change can be studied from this graph (Fig. 4). On the average, the observed points indicate a bit less oxygen consumption than was expected during the first five seconds of breath holding, but the rate apparently then becomes about as expected out to twenty seconds (Table 2). This may be due to an initial slackening of pulmonary blood flow accompanying the cessation of respiration,

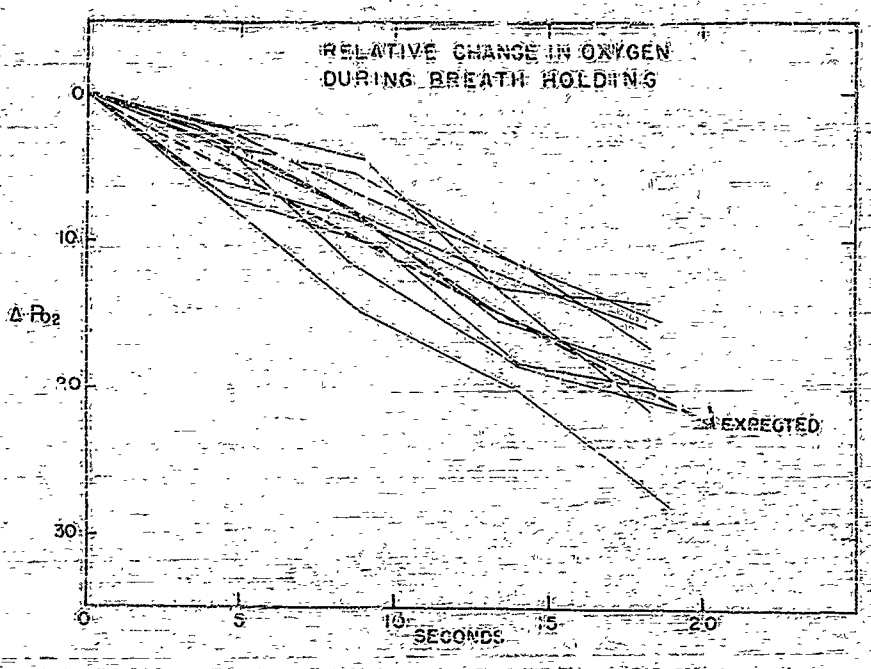

Figure 4

The rate of oxygen decline of ten breath holding experiments is compared to the rate of decline expected from knowledge of the metabolic rate, lung volume, and barometric pressure. Values for each subject have been reduced or increased to compare them with the mean expected rate of oxygen decline of the group. The mean bloodflow seems to decrease slightly during the early part of breath holding.

TABLE 2

Comparison of the Mean Change in P_{O_2}* During Breath Holding with the Change in P_{O_2} Expected from the Mean Alveolar Volume and Mean O_2 Consumption

Seconds of Breath Holding	5.45	10.21	15.12	20.11
Mean Change of P_{O_2}	3.71	8.47	14.79	19.18
Observed ΔP_{O_2} / Expected ΔP_{O_2}	.84	.88	.98	.93
Standard Error of this ratio	.12	.09	.06	.05

* Corrected for $\frac{F_{AN_2(o)}}{F_{AN_2(t)}}$

with subsequent reestablishment of bloodflow as compensatory ... ...sms come into play. This demonstrates the necessity for plotting pCO_2 ... pO_2 to gain an automatic correction for changes in bloodflow.

CONCLUSIONS

It seems fair to conclude from analysis of the data that t... ... slope of the breath holding curve is a little less than that of the mean R.C ... ...nd to explain this on the grounds that CO_2 has more volume to go into than ... has to leave from. It also seems fair to say that within the bounds of exp... ...al error the breath holding curve follows a course that is logarithmic in ... ...ture although this hypothesis would have to be tested over a large range and w... ...ma... more subjects to be absolutely sure. At least, the data is not incompatible ... theoretical analysis.

INSPIRATION

The alveolar gas point following inspiration is obtained by an... ...sis of a Haldane sample delivered rapidly at the end of a quick inspiration o... ...two l... ...rs from a spirometer (Table 3). This is plotted on the diagram to depict t... ...e dire... ...on that the pathway takes with inspiration, though it would be difficult to u... ...e it fo... ...ompuation of the tissue factor because of the undetermined amount of ga... ...exch... ...e with the blood

TABLE 3

Alveolar Point Following Rapid Inspiration a... Expira... ...n of Two Liters of Air (ATPS) After a Full E... ...ration

Subject	P_{AO_2}	P_{ACO_2}	...me from... ...nd of full expiration to e... ...full expiration
RS	118	31.3	...5
TM	111	33.1	.0
MS	118	30.3	.3
WF	115	23.8	.9
AD	117	26.4	2
KW	111	28.7	.0
MG	120	28.3	.9
HR	119	29.7	.4
RF	115	28.8	.9
Mean	116	28.9	.9

perfusing the lungs. However it can be pointed out that this ... ...s point' lies slightly above the line tangential to the breath holding curve at m... ...mum time. The significance of this is that instead of traveling straight along the ... an R.Q. line

[illegible] the inspired air point, the alveolar pathway during inspiration is probably [illegible] a line whose slope is less negative than that of the mean R.Q. line by the [illegible] alveolar volume to equivalent lung volume. The degree of deviation above [illegible] perfusion is the undetermined factor.

EXPIRATION AND INSPIRATION

[illegible] as breath holding is a condition in which there is no ventilation, and dilu[illegible] process in which one may conceive of negligible bloodflow, one can simi[illegible] picture expiration as a phase of the respiratory cycle in which there is no [illegible], and inspiration as a phase in which dilution is predominant. The alveolar [illegible] during expiration is similar to that found during breath holding except for a [illegible] curvature due to diminishing ratio of alveolar volume to equivalent lung [illegible] for CO_2. The alveolar pathway during inspiration is similar to that during [illegible] except for two opposing curvatures: Downward due to increasing ratio of [illegible] volume to equivalent lung volume for CO_2, and upward due to gas exchange [illegible] flowing blood, at increasing arterio-venous CO_2 content differences. Since [illegible] of dilution is short, the former seems to predominate, and the curve is [illegible] concave downward. These relationships are shown in Figure 5. The mean [illegible] exchange ratio is shown as a dotted line, and the ventilation-bloodflow [illegible] is drawn for reference. The loop formed by the expiratory and inspiratory

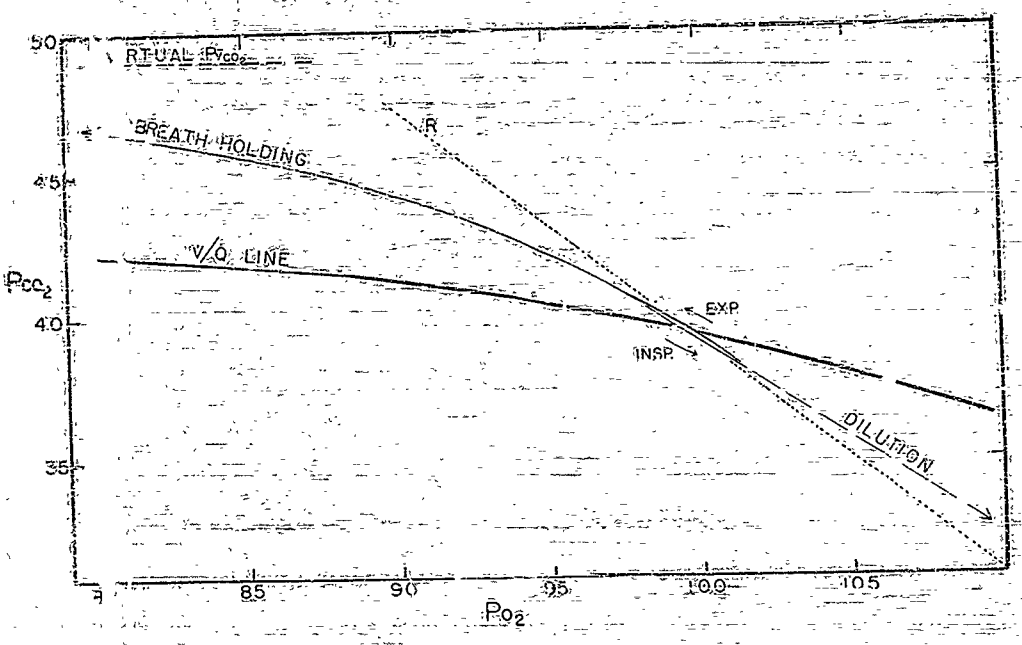

Figure 5

The pathway of departure from the mean alveolar point during breath holding, dilution, expiration and inspiration differs from the locus of mean alveolar points at different ventilation-bloodflow ratios, and from the line of the mean respiratory exchange ratio. Expiration is predominantly a process similar to breath holding, and inspiration to dilution, so that cyclical balance but no true equilibrium, is possible.

curves should enclose, but not pass through, the mean alveolar point as described by the intersection of the ventilation-bloodflow line with the line of the mean respiratory exchange ratio (R.Q. line). It is of interest that this loop is counter-clockwise as opposed to those found by continuous analysis of alveolar gas composition during work, hyperpnea, hypercapnia, and anoxia (3).

Computation of alveolar P_{O_2} throughout a normal respiratory cycle has been carried out so that the P_{O_2} can be plotted against the P_{CO_2} whose cyclical variations were described in a previous paper (4). Details of this computation may be found in the appendix. In essence, one determines the oxygen consumption that is compatible with the assumed CO_2 output and mean respiratory exchange ratio, then distributes this throughout a 4 second respiratory cycle divided into tenth of a second intervals. The alveolar volume is computed from a representative pneumotachogram, and the volume of oxygen present at each tenth of a second is divided by the alveolar volume to obtain the oxygen concentration. The ratio of alveolar volume to equivalent lung volume at the end of a normal expiration is assumed to be .85. This ratio changes during the cycle. The mean respiratory exchange ratio is assumed to be .81. The cycle thus obtained is plotted in Fig. 6. It may be noted that during the first part of inspiration the curve continues to follow the expiratory direction, due to inspiration of the gas in the dead space. However the 'concave downward' trend of the curve is no longer followed. As dilution takes place, the curve moves rapidly back toward

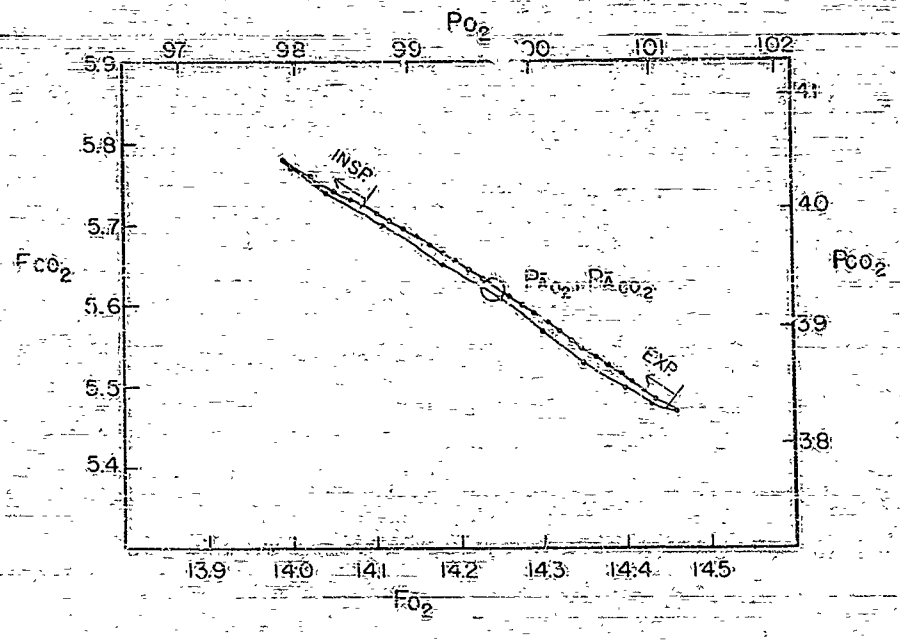

Figure 6

Changes in alveolar O_2 and CO_2 were calculated for a normal respiratory cycle, plotted for each tenth of a second. The loop is based on observations made by breath holding and by inspiration of air. For details of calculation, see the appendix.

its starting point. Each tenth of a second is represented by a point on the curve. This is the same cycle that is represented in Fig. 5 at the overlapping of the breath holding curve and dilution curve, and demonstrates the similarity of expiration to breath holding and inspiration to dilution.

One may picture a slightly more horizontal loop in alveoli with a lower ventilation-bloodflow ratio, and a more vertical loop in areas with a higher ratio than the mean. Mixtures of gases from two regions with unequal ventilation-bloodflow ratios would presumably lie on lines connecting synchronous alveolar points on the respective loops of the regions, and asynchronous emptying of two such regions would disclose points on lines connecting these loops, and along the connecting lines a distance proportional to the fraction of gas from either region. Expired gases would appear as a line transecting these connecting lines in order.

APPENDIX

Computation of P_{CO_2} during a representative respiratory cycle.

1. The fluctuations of O_2 are calculated to accompany a similar calculation for CO_2 in a previous communication (4). The respiratory quotient is assumed to be .81, and therefore the oxygen consumption to be 480 cc BTPS per minute, or .800 cc per tenth of a second.

2. The mean alveolar P_{CO_2} computed from the equation:

$$\bar{R} = \frac{(.791)(P_{ACO_2})}{(.209)(B-47-P_{ACO_2}) - P_{AO_2}}$$

is 101 mm Hg., or 14.21% at B = 747. This occurs shortly after mid-expiratory time.

3. Construct a table showing time in tenths of a second; alveolar volume at this time (computed as .85 of equivalent lung volume for CO_2 at the end of a normal expiration), taking tidal volume as compatible with the alveolar ventilation; volume of O_2 inspired via the trachea; change in O_2 due to metabolic rate either in cc BTPS per tenth of a second or in % of dry gas per tenth of a second; O_2 inspired due to the respiratory exchange ratio; and volume of O_2 or $\%O_2$ present at the end of the tenth of a second.

4. The table is filled in starting at the 'mean alveolar point' assumed for computation using the steady state equations. One may compute the expiratory part of the cycle first, then the inspiratory part, taking into account the air dragged in during inspiration due to the respiratory exchange ratio. The loop thus formed is tangent to the mean alveolar point. It probably surrounds the latter in the lungs, but the exact relationship of the loop to the mean point is not determined by the above procedure. It is possible that the mean point is at the center of gravity of the loop.

APPENDIX (cont.)

Time	Alv. Vol.	Vol. O_2 insp.	Metabolic ΔO_2 / $\Delta\%O_2$	O_2 from R.Q.	Corrected New O_2	as $\%O_2$
0	5100	1.853	-.800 cc.		719.439 cc.	14.07
.1	5113	.998	.800		719.637	14.05
.2	5120	2.280	.800		721.117	14.03
.3	5136	3.56	.800		723.887	14.02
.4	5151	5.53	.800		728.607	14.00
.5	5200	7.12	.800		734.927	13.99
.6	5250	11.24	.800	.16	745.527	14.04
.7	5307	13.96	.800	.21	757.897	14.11
.8	5369	13.56	.800	.22	770.897	14.18
.9	5434	12.54	.800	.21	782.847	14.25
1.0	5494	11.70	.800	.19	793.037	14.30
1.1	5550	11.29	.800	.19	804.617	14.35
1.2	5604	10.03	.800	.16	814.007	14.40
1.3	5652	8.14	.800	.13	821.477	14.43
1.4	5691	5.22	.800	.09	826.997	14.46
1.5	5716	2.09	.800	.03	827.307	14.45
1.6	5726		-.0140%	1.59 cc.	14.4344%	
1.7	5718		.0140		14.4204	
1.8	5698		.0140		14.4064	
1.9	5673		.0141		14.3923	
2.0	5637		.0142		14.3781	
2.1	5560		.0143		14.3638	
2.2	5514		.0145		14.3493	
2.3	5446		.0147		14.3346	
2.4	5375		.0149		14.3197	
2.5	5308		.0151		14.3046	
2.6	5215		.0152		14.2894	
2.7	5206		.0154		14.2740	
2.8	5169		.0155		14.2585	
2.9	5140		.0156		14.2429	
3.0	5118		.0156		14.2273	
3.1	5108		.0157		14.2116	
3.2	5101		.0157		14.1959	
3.3	5097		.0157		14.1802	
3.4	5096		.0157		14.1645	
3.5	5100		.0157		14.1488	
3.6	5100		.0157		14.1331	
3.7	5100		.0157		14.1174	
3.8	5100		.0157		14.1017	
3.9	5100		.0157		14.0860	
4.0	5100					

SUMMARY

1. Alveolar P_{CO_2} plotted against P_{O_2} during breath holding follows a logarithmic curve whose asymptote is virtual venous P_{CO_2} and whose negative exponential constant is equal to the mean respiratory exchange ratio times the alveolar volume divided by the equivalent lung volume for CO_2 and the mean arterio-venous P_{CO_2} difference. The initial slope of this curve is the mean respiratory exchange ratio times the ratio of alveolar volume to equivalent lung volume for CO_2. The latter ratio is estimated to be between 0.7 and 1.0.

2. The P_{O_2} - P_{CO_2} pathway during inspiration is essentially along a line toward the inspired air point but with a slope similar to that of the initial slope of the breath holding curve described above.

3. The pathway of P_{CO_2} plotted against P_{O_2} during a theoretical respiratory cycle, based on observations, is a counterclockwise loop that is elongated along the direction of the initial part of the breath holding curve, and narrow in the direction transverse to this. This loop encloses but does not pass through the mean alveolar point.

4. Mean alveolar P_{O_2} and P_{CO_2} are best represented by an alveolar sample shortly after mid-expiratory time. However no single sample can be expected to yield the exact mean of both gases at the same time.

The authors wish to gratefully acknowledge the technical assistance of Miss Eileen Ginter.

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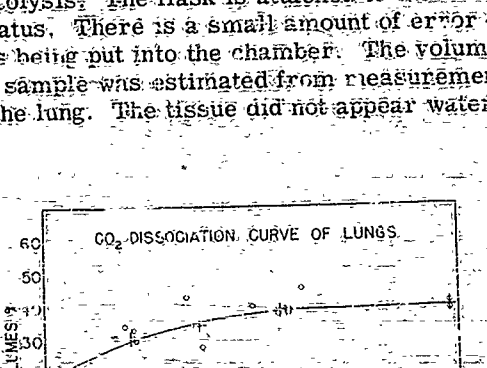
CO_2 DISSOCIATION CURVE OF LUNG TISSUE

by

W. O. Fenn, A. B. DuBois[1] and A. G. Britt

The volume of CO_2 per hundred grams of lung tissue should depend on the P_{CO_2} of the alveolar air, the degree of equilibration of the gaseous with the liquid and solid phases, and the chemical composition of the liquid and solid phases (buffering).

Apparatus used to vary the alveolar P_{CO_2} in the bloodless lungs of dogs consisted of a tracheal cannula attached to a Haldane sampling tube and bulb filled with acidified water for pumping the air in and out of the lungs. A cannula in the femoral vein was used to perfuse the living animal with two to four liters of isotonic saline or unbuffered Ringer's solution, the blood being allowed to flow out of the carotid artery at an equal rate. The animals had been used for student experiments not involving the chest. At the time of death, the blood was found to have been replaced about three times, and there was little evidence of hemoglobin in the perfusate. The animal was then 'rebreathed' with air or CO_2 in air for thirty to sixty seconds. Two samples of lung tissue were taken for analysis for total CO_2 content according to the method of Danielson and Hastings (1). This method uses a small flask containing the weighed aliquot of tissue in a solution that inhibits glycolysis. The flask is attached to the side arm of a Van Slyke manometric apparatus. There is a small amount of error in escape of CO_2 from the tissue while it is being put into the chamber. The volume of CO_2 present in the alveolar air of the sample was estimated from measurement of the density of the remaining part of the lung. The tissue did not appear waterlogged, and the mean density was 0.6.



This Dissociation Curve of Lung Tissue was obtained by equilibrating dogs lu[illegible] with different mixtures of CO_2 and air, analyzing the resultant mixture for P_{CO_2}, and the tissue for CO_2 content by the method of Danielson and Hastings.

Data is presented in the form of a graph with CO_2 content in volumes CO_2, cc. STPD, per hundred grams of tissue, wet weight, plotted against P_{CO_2} as measured

1 This work was done during the tenure of a Life Insurance Medical Research Fellowship.

by analysis of the equilibrated air mixture on the Scholander micrometer for gas analysis apparatus. Means of groups of points are indicated by crosses, and a free-hand curve drawn to the best fit. This curve shows an increase in the CO_2 content of the tissue with increase in alveolar P_{CO_2}. The number of points is insufficient to determine the exact slope of the curve. This dissociation curve is not unlike that of plasma (2) and muscle (3).

The conclusion based on this experiment is that bloodless lung takes up a considerable amount of CO_2 within a 30 second period of equilibration with alveolar air. It would seem that this is not a negligible factor in evaluating changes in gas tensions during breath holding or inspiration.

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I. BREATH HOLDING STUDIES: RELATIONSHIP TO LUNG VOLUME

by

John F. Muxworthy Jr.

The relation of lung volume to breath holding was stimulated by Monod and Cara (1) who proposed a method for the determination of residual air by relating the time of a maximum voluntary apnea to maximum and minimum lung volumes. They concluded that the length of time of apnea was a linear function of the lung volume. Thus by plotting the maximum voluntary breath holding times obtained at zero and maximum vital capacity against these respective lung volumes the residual air volume could be derived by extrapolation. Vacca and Boeri (2,3), however, found as a result of a large number of experiments that this relationship was far from linear, thus invalidating this method of residual air determination. Since the chemical composition of the arterial blood and the alveolar gas has a profound effect upon the breath holding time and since these would be altered by any change in lung volume larger than the functional residual air capacity, it seems hardly likely that a linear relationship would be obtained. Furthermore, one would not expect the breath holding time to be zero at zero lung volume since the mixed venous blood coming into the lungs would have to travel unchanged to the chemoreceptors or to the respiratory center before it could cause the stimulus necessary to terminate the voluntary apnea. Thus, one might expect that the breath holding time at zero lung volume would not be zero, but at least equal to the circulation time from the lungs to the chemoreceptors or the respiratory center. In order to investigate these relationships the alveolar gas concentrations at the end of voluntary apnea were studied at various lung volumes in order to ascertain the magnitude of the chemical stimulus under these conditions. In addition the lung to ear circulation time was determined in order to approximate the time needed for the blood to travel from the lungs to the respiratory center.

METHODS

Four trained male subjects served in all experiments. Lung volumes were determined by the modification of the Lundsgaard and Van Slyke technique (4). All lung volumes were converted to B.T.P.S.

During the test the subject was seated. The breath was held as long as possible and at the breaking point all of the air was expired through a long one inch tube into a spirometer. From the volume of the expired air and the known residual air volume the absolute total lung volume could be obtained at which the breath was actually held. The last portion of the expired air was trapped by a stopcock and immediately analyzed for oxygen and carbon dioxide by the automatic measuring device (5).

The normal lung to ear circulation time was obtained with the Millikan ear oximeter. This time began with the deep inspiration of nitrogen gas and ended with the first drop in oxygen saturation recorded on the galvanometer. The results are shown in Tables 1 and 2 and in Figs. 1 and 2.

TABLE 1

Lung Volumes, Circulation Time, Normal Alveolar Air Concentrations and Breath Holding Time (B.H.T.) at the Functional Residual Capacity Volume for the Four Subjects

Subject	Bar. mm Hg	Residual Air V. ml	Expiratory Reserve ml	Vital Capacity ml	Total Capacity ml	Circulation Time-sec	Alveolar pCO_2	Alveolar pO_2	B.H.T. sec.
A. O.	746	1325	1855	5040	6365	8.5	40	93	55
H. R.	749	2325	2240	6177	8402	9.0	38	98	83
C. C.	745	1373	1552	4783	6156	8.0	42	87	30
J. M.	741	1902	1950	5707	7609	8.3	46	85	38
Mean	746	1706	1899	5426	7133	8.7	41	90	51

TABLE 2

Breath Holding Time and Alveolar Air Concentrations at the Breaking Point at Various Total Lung Volumes for the Four Subjects. The Lung Volumes Marked With Asterik Were Obtained by Inspiring Previously Collected Alveolar Air.

Subject	Lung Vol. ml.	Time sec.	Alveolar pCO_2	Alveolar pO_2	Bar	Subject	Lung Vol. ml.	Time sec.	Alveolar pCO_2	Alveolar pO_2	Bar
A. O.	1919	49	47	49	745	H. R.	3335	77	51	49	739
	1952	50	48	45	746		3505	70	50	52	749
	2110	51	49	45	746		3625	71	50	60	749
	2425	45					4220	80	50	54	749
	2915	57	48	50	745		4445	86	48	60	739
	3060	48	52	50	745		5525*	82	50	60	749
	3165	63	50	45	745		5575*	88	51	58	739
	3185	61	52	47	746		6425*	92	51	60	749
	3225	53					6555*	94	52	52	739
	4755*	71	50	52	745						
	4905*	80	53	45	746	J. M.	2120	29			
	6085*	74	53	57	746		2120	30			
							3723	34	52	64	741
C. C.	2138	26	50	67	749		3743	34			
	2234	22	45	67	745		3923	45			
	2234	28	46	60	745		4063	34	50	62	741
	2354	28	46	67	749		4063	37	52	62	741
	2963	30	45	68	745		5578*	47*	53	61	741
	3113	30	48	66	749		5583*	43*	50	67	747
	4433*	43	47	67	749		6763*	58*	53	59	741
	5043*	43	48	63	745		6903*	56*	51	61	747

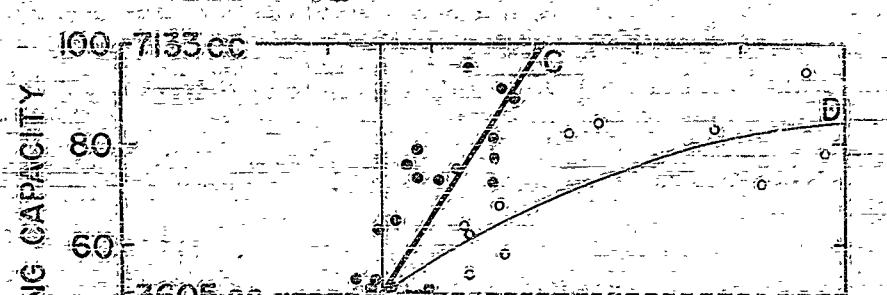

Figure 1

The maximum breath holding time plotted against the total lung volume; average of four subjects. The lung volumes are expressed as % of total lung capacity. The breath holding time at the end of a normal tidal volume averaged 51 seconds and is expressed as 100% breath holding time. The solid circles represent experiments where the initial alveolar gas concentration was kept constant and line A-C represents the best fit. The open circles (line B-D) represent experiments where the initial alveolar concentration was altered by filling the lungs with room air. The difference between line BC and BD indicates the chemical inhibition produced by inspiring room air and altering the initial alveolar air concentrations. Ct represents the lung to ear circulation time.

DISCUSSION

It is clear that in order to evaluate the effect of lung volume, per se, on the breath holding time the initial alveolar concentration of O_2 and CO_2 at the beginning of apnea at any lung volume must be the same. At lung volumes smaller than the resting level this can be achieved by quickly blowing out a certain volume of the expiratory reserve. At lung volumes larger than the resting level the inspired air will reduce the alveolar CO_2 and increase the O_2 concentration. This chemical change, alone, will greatly effect the breath holding time and result in a lung volume - breath holding time relationship as indicated by the dotted line B--D in Fig. 1. This trend has been established in more detail by Vacca and Boeri (2,3) and is largely accounted for by the inhibiting effect of lowered alveolar CO_2 and increased alveolar O_2.

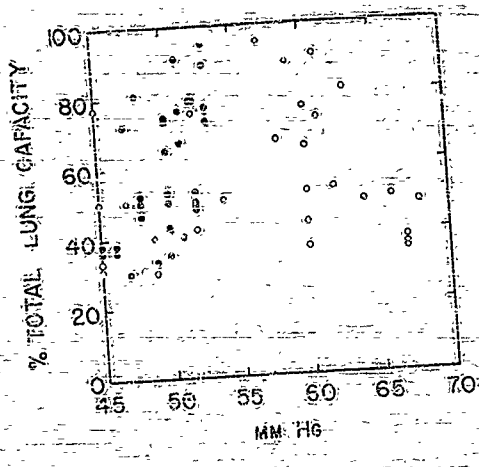

Figure 2

The alveolar gas concentration at the end of maximum breath holding are plotted against the total lung volume. Open circles represent oxygen, solid circles represent CO_2.

Therefore, to prevent alterations of the resting alveolar gas concentrations at lung volumes greater than the resting volume, aveolar air (previously collected in a spirometer) was inspired instead of room air. Thus the initial chemical stimulus was assumed to be identical at all lung volumes tested and one deals essentially with the effect of lung volume per se. The volume - time relationship under these conditions is indicated by the solid circles in Fig. 1. This relationship was assumed to be linear and the best fit is represented by line A-B-C. It is of interest to note that not even this line intercepts the zero volume curve at zero time as Monad and Cara had originally postulated, nor at the lung brain circulation time (C.T. - Fig. 1) as discussed above. On the basis of the intercept of line A-B-C- one might conclude that a direct shunt of all the mixed venous blood directly into the systemic circulation would still allow a voluntary apnea of 10 seconds. In any event, it strongly suggests that as method for the determination of the residual air volume the method of Cara and Monad is quite unreliable even if the initial gas concentration at the various lung volumes prior to apnea are kept constant.

In Fig. 2 the pCO_2 and the pO_2 of the alveolar gas at the end of breath-holding are plotted against the total lung volumes. There is very little, if any, correlation of the oxygen concentrations in respect to different lung volumes. However, it appears that there is a small, but definite increase in the pCO_2 at the breaking point with the larger lung volumes.

The greater scatter of the oxygen concentrations suggest as Otis et al (6) have pointed out that when breathing air at normal barometric pressures the CO_2 concentration is the dominant factor in achieving the breaking point. The greater CO_2 concentration associated with larger lung volumes is of interest. This may be due to the greater activity of the pulmonary stretch receptors which aid the apnea by inhibition of the respiratory center (Hering-Breuer reflex) and reduce breath holding time at small lung volumes by stimulating the center.

SUMMARY

In four subjects the maximum breath holding time and the concentration of the alveolar gases at the breaking point were studied when the breath was held at various lung volumes. In order to have the same initial chemical stimulus a procedure was arranged in such a manner that the alveolar air concentrations at the beginning of apnea was identical at all lung volumes. Under these conditions there appears to be a linear relationship between lung volume and breath holding time. However, the extrapolation of this relationship does not intercept the coordinates of time and total lung volume at zero thus rendering this method for the determination of residual air volume of doubtful value.

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II. BREATH HOLDING STUDIES: THE CARDIO-VASCULAR RESPONSE

by

John F. Muxworthy Jr.

There exists many studies of the cardio-vascular response to various alveolar O_2 and CO_2 concentrations. Schneider (1) states that in man small increases in CO_2 in the lungs (up to 3%) cause dilation while with a stronger concentration a constriction occurs. It was suggested that the dilation is due to nervous action while the constriction is a direct stimulation of the muscle of the arterioles. According to Itami (2) constriction of the fore limb vessels in animals accompanies a general increase in the blood pressure caused by an increase in CO_2. Schneider (3) also states that neither the hand volume nor the rate of blood flow changes while breathing nitrogen with low O_2 concentration. However, rebreathing air without CO_2 absorption so as to raise the pCO_2 and lower the pO_2, the blood pressure increased and the hand volume as well as the rate of flow decreased. In some of the latter studies it was observed that as the concentration of CO_2 gradually increased the hand volume first increased and then decreased.

Breath holding involves similar alveolar O_2 and CO_2 changes and it is the purpose of these experiments to demonstrate the cardio-vascular responses. They have been approached by measurements of the pulse volume, the total finger volume, the rate of blood flow into the finger, the pulse rate, the systolic and the diastolic blood pressures.

METHODS

The breath was held for these experiments at the end of a normal expiration by five trained subjects who were at rest and in a supine position. The pulse volume, total finger volume, the rate of flow and the pulse rate were obtained by a finger plethysmograph and recorded photographically after the method of Fenn et al (4). The blood pressures were recorded by an automatic commercial blood pressure machine manufactured by the Cambridge Instrument Co. This instrument made use of a double cuff around the upper arm and recorded intermittent pressures, the systolic during one experiment and the diastolic during another similar experiment.

DISCUSSION

In order to compare an average the values obtained from the different subjects, the readings for the pulse volume, rate of flow and total finger volume are expressed in percent of the normal resting values. Since the individual time of breath holding varied, the maximum time for the individual was designated as 100% and intermediate points referred to as percentages. The results are recorded in Table 1.

The cardio-vascular response to breath holding is seen graphically in Figs. 1 and 2. In Fig. 1 it should be noted that the blood pressure appears to drop as soon as the apnea is terminated. This, however, is not the case as the technique used to measure the blood pressures was not fast enough to give the proper time relationship at the end of breath holding. On close examination of individual records it is

TABLE 1

Average values obtained from five subjects during rest, breath holding and recovery. Breath holding and recovery times are expressed as percent. The maximum breaking point time = 100. Systolic and Diastolic Blood Pressure, mm Hg; Rate of Finger Flow, Pulse Volume as percent of resting value; Finger Volume - percent decrease; Heart Rate per minute; S.D. - Standard Deviation.

		Rest	Breath Holding				Recovery				
Time			20	40	60	80	100	20	40	60	80	100
Systolic	B.P.	126	126	131	131	136	141	137	133	130	127	126
	S.D.	12.6	11.6	13.4	14.0	15.2	15.3	16.2	13.4	15.2	14.3	13.1
Diastolic	B.P.	64	66	69	72	77	80	78	76	73	69	66
	S.D.	12	11.6	10.7	10.9	12.2	14.6	14.8	13.6	11.9	10.3	10.1
Rate of Flow		100	61	62	52	49	35	27	51	74	87	97
	S.D.	0	19.3	19.3	19.2	20.8	11.8	10.6	27.4	16.9	10.6	7.1

	Rest	Breath Holding				Recovery					
Time		25	50	75	100	25	50	75	100	125	150
Pulse Vol.	100	77.5	77.1	62.9	56.2	56.8	63.9	101.8	100.3		
S.D.	0	18.9	15.7	10.0	12.0	13.1	6.4	20.2	6.72		
Finger Vol.	0	.093	.086	.18	.266	.35	.368	.29	.23	.16	.055
S.D.	0	.073	.089	.09	.113	.183	.284	.226	.171	.139	.091
Heart Rate	71	69	71	59	67	66	64	61	63		
S.D.	7.4	5.3	6.6	7.8	13.9	12.2	9.9	7.5	9.7		

seen that the pressure does not fall immediately as is indicated in Fig. 1 but remains elevated about the same period as the rate of flow and the pulse volume remain changed as a result of the apnea. The total response, then, as shown in these two figures indicate a vasoconstriction and a bradycardia as the period of apnea progresses. These trends are reversed about 8 to 10 seconds after the breaking point has been reached.

The explanation for this lag maybe twofold. Assuming the constriction to result from the increased CO_2, then before dilitation can occur the blood with decreased CO_2 as a result of the termination of the apnea must travel from the lungs to the arterioles or to the vaso-motor centers. The time lag involved is of the proper order. Secondly, it has been shown by DeLalla (5) that peripheral vaso-constriction follows deep inspiration as well as expiration, both of which take place after the breaking point has been reached. His proposed explanation is that during inspiration reflexes arise from the right auricle and the large intrathoracic veins due to the sudden decreased intrathoracic pressure and that during expiration reflexes arise from the large extrathoracic veins due to the increased intrathoracic pressure. Possibly both

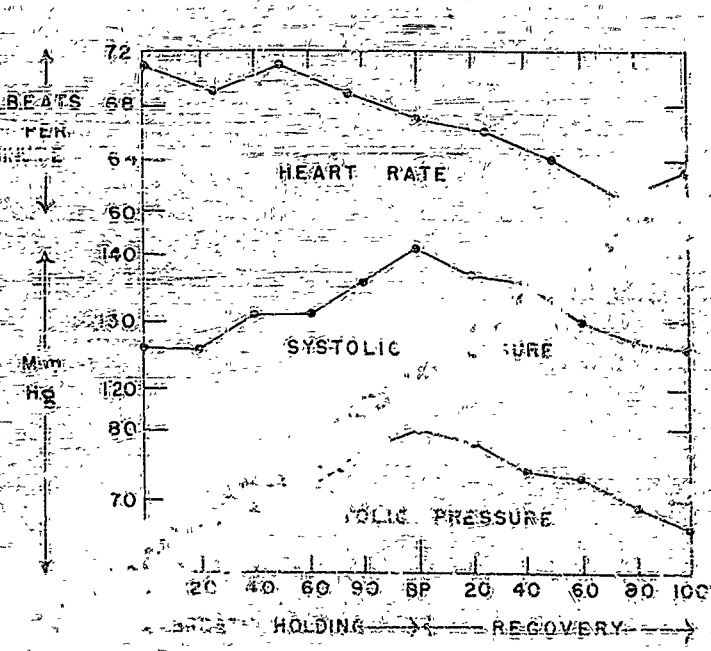

Figure 1

The heart rate, systolic and diastolic blood pressure are plotted during breathing and recovery. The time of breath holding is expressed in % with the maximum breath holding time (B.P.) equal to 100%.

of these factors, the CO_2 action as well as the respirator reflex, account for the maintained vaso-constriction after the breaking point has been reached.

As the blood pressure increased the heart rate decreased, which may be the result of vagal stimulation set up through the pressor receptors in the aorta and carotid sinuses.

SUMMARY

1. Measurements were made of the heart rate, the systolic and diastolic blood pressure, the rate of flow of blood into the finger, the pulse volume and the total finger volume during breath holding and during recovery.

2. The systolic and diastolic pressures increased with breath holding the heart rate decreased. After the breaking point recovery of the pressures was gradual while the heart rate kept on diminishing for a period nearly equal to the breath holding.

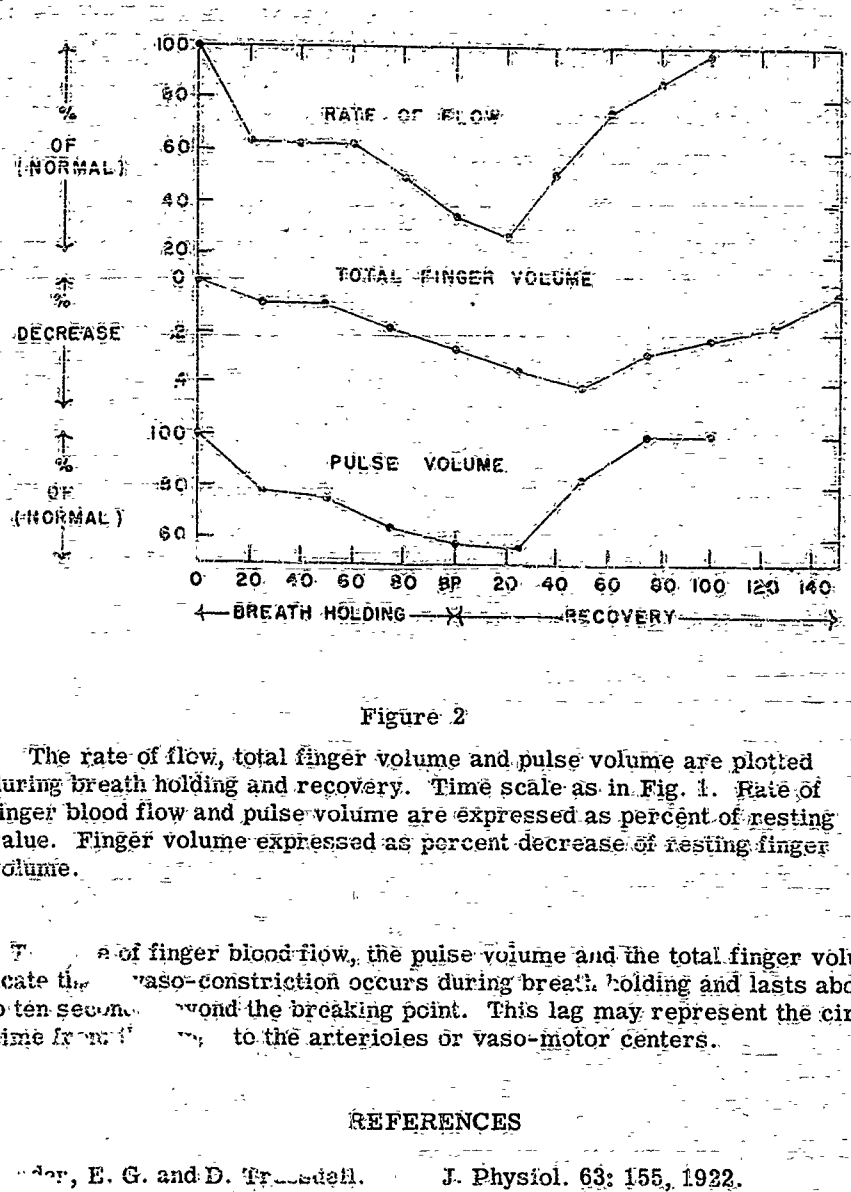

Figure 2

The rate of flow, total finger volume and pulse volume are plotted during breath holding and recovery. Time scale as in Fig. 1. Rate of finger blood flow and pulse volume are expressed as percent of resting value. Finger volume expressed as percent decrease of resting finger volume.

3. T[illegible]e of finger blood flow, the pulse volume and the total finger volume all indicate th[illegible]vaso-constriction occurs during breath holding and lasts about eight to ten seconds beyond the breaking point. This lag may represent the circulation time from [illegible] to the arterioles or vaso-motor centers.

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ALVEOLAR GAS CHANGES DURING BREATH HOLDING[1]

A. B. OTIS, H. RAHN AND W. O. FENN

Although there are in the literature numerous studies of the maximum time that the breath can be held under various conditions (1), there is little information available regarding the changes in alveolar gas composition during breath holding. The composition of the alveolar air at the end of the involuntary apnoea (not the maximum voluntary apnoea) produced by two minutes of hyperventilation has been measured by Douglas and Haldane (2) with various concentrations of oxygen in the air inspired during the period of forced breathing. The same authors (3) as well as Hill and Flack (4, 5) have compared the alveolar compositions existing at the end of maximum breath holding when air and when pure oxygen were previously breathed. Ferris *et al.* (6) have measured the pCO_2 and pO_2 of the arterial blood at the 'breaking point' and recognize these factors as interrelated stimuli for termination of breath holding.

It is the purpose here to present data showing the alveolar gas exchange during periods of breath holding following the breathing of various inspired oxygen tensions and to consider the factors determining the maximum duration of breath holding.

METHODS

In all cases the breath was held at the end of a normal expiration in the sitting position. The same eight trained subjects[2] were used in all experiments. The breath was held as long as possible and the expiratory reserve was then vigorously blown through a large stopcock into a rubber tube two meters long and 2.5 centimeters in diameter. As soon as the expiration was complete the stopcock was closed to trap the sample of alveolar air in the tube. A small side arm just below the stopcock delivered the sample to the oxygen and carbon dioxide meters (7) where it was immediately analyzed.

Low oxygen tensions in the inspired air were obtained in a high altitude chamber by going in succession to simulated altitudes of 8, 12, 16 and 18 thousand feet. The subjects, who wore ear oximeters, remained at each altitude for about two minutes and delivered two samples which were analyzed at that altitude. Upon return to ground level the breath-holding test was repeated.

Oxygen tensions higher than normal were obtained by breathing 32 per cent

[1] Work done under contract recommended by Committee on Medical Research between the Office of Scientific Research and Development and the University of Rochester, and under contract with the Air Materiel Command, Wright Field.

[2] We wish to acknowledge the fine cooperation of the members of Civilian Public Service Unit No. 115-R who served as subjects and technicians during these experiments.

and 45 per cent oxygen in nitrogen and 100 per cent oxygen from large spirometers at ground level for ten minutes before the breath was held. Each test was repeated twice or until reliable checks were obtained upon repeat readings.

RESULTS

At ground level, and particularly at the higher altitudes, there was no hesitation on the part of the subjects in deciding exactly when further apnoea was impossible. On the other hand, at the two highest oxygen concentrations it was often rather difficult to decide when the real breaking point had been reached. While holding the breath at these high oxygen tensions, the subjects experienced involuntary contractions of the respiratory muscles which became increasingly violent and rapid. At first they involved the diaphragm and later the intercostals and accessory breathing muscles. Simultaneously the subject experienced sensations of increasing warmth with flushing of the skin and sweating, particularly of the forehead and of the palms of the hand. Even so the first minute of breathing pure oxygen frequently seemed more uncomfortable than the last minute.

At 18,000-foot altitude all subjects came very close to fainting. Some actually lost postural control momentarily with involuntary swaying of the body or head. Two men, however, were able to carry out the breath-holding maneuver successfully at 20,000 feet.

A summary of the average breath-holding times for eight subjects at 10 different tensions of inspired oxygen is given in table 1. Data are also given for ear oximeter readings at the breaking point, mean R.Q during the period of apnoea and terminal values of alveolar pCO_2 and pO_2. In general the higher the O_2 tension, the higher the CO_2 at the breaking point and the longer the period of voluntary apnoea. The observed arterial saturations are all slightly lower than the values calculated from the alveolar gas tensions, presumably because the oximeter fall suddenly at the time of forcible expiration, as if from some circulatory disturbance, and we recorded only the lowest values.

The data relating to composition of the alveolar gas are graphically depicted in figure 1 by plotting them on a pCO_2-pO_2 diagram (8). The numbered circles indicate the average breaking points in the various experiments and form the basis for constructing the breaking point curve. This curve also adequately fits the breaking points determined from analysis of arterial blood by Ferris *et al.* (6). It is also similar in shape to the curve of Douglas and Haldane (2) showing the points at which involuntary apnoea following hyperventilation ceases, but is located higher on the diagram. The starting point for each test is indicated by the appropriate pCO_2-pO_2 value on the normal alveolar gas curve (constructed from our own data). The dotted lines leading from the starting points to the breaking points indicate the presumed time course of the alveolar gas changes during the breath-holding period. (The actual time course is known in only three subjects and will be discussed below.) Except for the lower tensions of inspired oxygen, the slopes of these lines become less with time, because the O_2 uptake from the lungs remains relatively constant while the CO_2 output di-

TABLE 1. SUMMARY OF ALVEOLAR GAS TENSIONS AND OTHER DATA IN BREATH HOLDING (B.H.) EXPERIMENTS

(1) Experiment no.	1	2	3	4	5	6[2]	7	8	9	10
(2) No. of subjects	8	8	8	8	8	8	8	8	6	7
(3) No. of expts.	12	16	16	16	16	15	22	15	13	14
(4) B-47 in mm. Hg	332	385	436	517	697	697	702	700	691	694
(5) Altitude in thousands of feet	18	16	12	8	0.5	0.5	0.5	0.5	0.5	0.5
(6) Inspired pO_2	69	76	91	108	146	146	147	227	317	694
(7) Inspired O_2%	Air	Air	Air	Air	Air	Air	Air	22.4	45.9	100
(8) Alveolar pO_2 before breath hold	36	41	50	62	104	104	104	187[1]	277[1]	656
(9) Alveolar pCO_2 before breath hold	30	33	37	37	38	38	38	38	38	38
(10) Alveolar pN_2 before breath hold[3]	266	291	349	418	555	555	560	475	376	0
(11) Alveolar pO_2 after breath hold	28.0	31.1	38.1	44.2	62.7	45.6	52.1	72.5	157	628[3]
Std. dev. ±	1.0	2.9	1.4	3.0	9.9	6.7	9.0	16.0	34.2	3.9
(12) Alveolar pCO_2 after breath hold	38.6	42.3	45.6	46.9	50.1	48.3	50.2	57.5	62.6	66.3
Std. dev. ±	2.8	2.6	1.9	1.2	1.5	3.1	1.7	4.4	5.6	3.9
(13) Alveolar pN_2 after breath hold[5]	265	292	354	426	584	603	600	570	471	0
(14) Duration of B.H. in seconds	23	25	27	30	35	59	50	92	106	153
Std. dev. ±	6.4	3.7	6.4	8.7	4.4	18.3	17.1	28.9	38.9	53.5
(15) HbO_2% by oximeter	48	51	61	71	87	70				
(16) HbO_2% by calculation	55	58	67	77	90	78	86	92		
(17) Lung volume after B.H., liters	3.0	3.0	2.97	2.97	2.85	2.76	2.80	2.50	2.40	2.42[3]
(18) O_2 intake rate during B.H., cc/min.	73	84	109	143	264	220	230	289	300	
(19) Average R.Q. during breath hold	1.07	.93	.57	.48	.22	.10	.16	.08	.08	

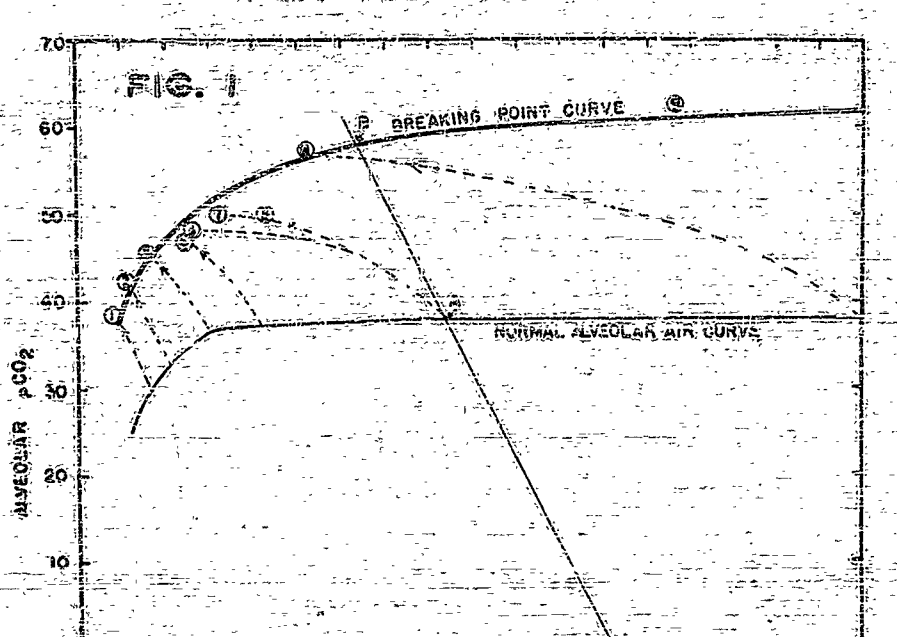
[1] Assumed 40 mm. Hg less than inspired pO_2 in row 6.

[2] Observations made immediately after hyperventilation caused by previous 'ascent' to altitude.

[3] Calculated as row 4 minus row 12. Measurements on the O_2 meter are very inaccurate at this level.

[4] Calculated by equation 6 assuming Q = 0.1.

[5] pN and p'N were calculated by subtracting the CO_2 and O_2 tensions from B-47 in row 4.



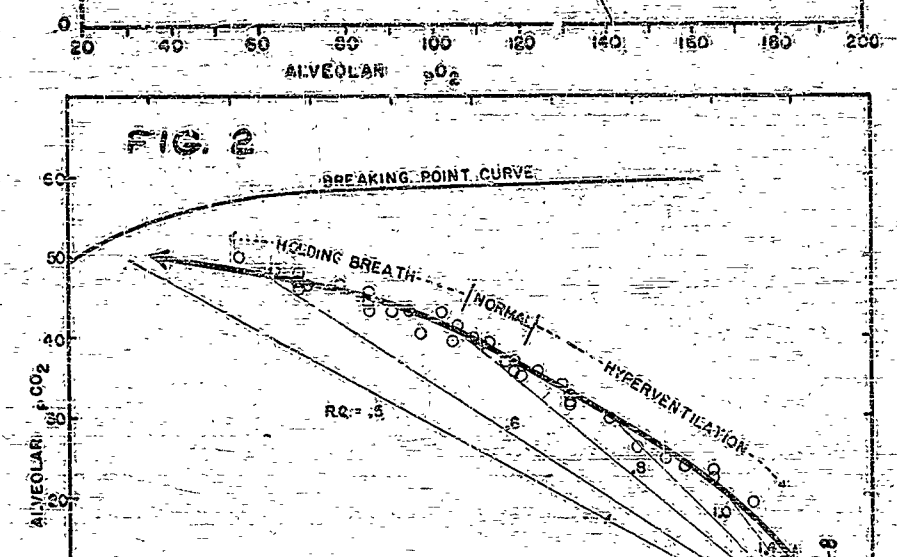


FIG. 1. THE PRESUMED COURSE OF CHANGE in alveolar gas composition during breath holding under various conditions.

FIG. 2. THE ALVEOLAR PATHWAY during breath holding and during hyperventilation.

minishes. This is explained by the fact that although an ample gradient for transfer of O_2 from lungs to blood exists throughout the breath-holding period, the gradient for transfer of CO_2 in the opposite direction becomes progressively less favorable owing to the ever increasing pCO_2 in the lungs.

At the lower inspired O_2 tensions, however, the slopes of these dotted lines are steeper in general and do not fall off much with time. At these O_2 tensions the alveolar diffusion gradient for oxygen is so much less than normal that the O_2 uptake from the lungs is lower and more nearly equal to the CO_2 transfer. Another manifestation of these processes is that the rate of change of lung volume during breath holding is greater the higher the pO_2 of the inspired air (9).

The dotted lines in figure 1 represent the presumed time course of the alveolar air composition while breathing air at different altitudes. The time course depends, however, not only upon the initial tension of oxygen but also on the percentage of oxygen. Point A in figure 1 represents the alveolar air at ground level, breathing air. The same tensions of oxygen and carbon dioxide can be obtained by breathing pure oxygen at an altitude of approximately 34,000 feet. In this case when the breath is held, the composition of the alveolar air must remain somewhere on the line AB, this being the diagonal for an R.Q. of 1.0 where $pCO_2 + pO_2 = 142$ (8). The carbon dioxide tension at point B is far higher than at point A, breathing air. One of our subjects carried out this experiment and found that the pCO_2 at the breaking point was 48 mm breathing air at ground level but was 62.5 mm at 34,000 feet breathing pure oxygen. Likewise the pO_2 was higher and the period of voluntary apnoea longer in the latter case. This experiment confirms, therefore, the theoretical expectations. If the lungs contain pure O_2, a passage of O_2 into the blood causes a decrease in volume but no change in O_2 tension. In the presence of a large amount of N_2, however, a decrease in volume due to diffusion of O_2 results chiefly in increasing the pN_2 so that the O_2 tension becomes much less than when pure O_2 is breathed. This would tend to decrease the amount of CO_2 which can be tolerated and should shorten the breath-holding time. At the same initial oxygen tension, therefore, the greater the percentage of oxygen the less the decrease in pO_2 for the same O_2 consumption. As we have shown elsewhere (8) the R.Q. diagonals deviate less and less from the R.Q. = 1 line as the O_2 percentage increases until at 100 per cent O_2 they all coincide. The breath-holding experiment referred to is a manifestation of this phenomenon. The observation of Brown (10) that the breath can be held longer at 30,000 feet on pure O_2 than at ground level on air is also consistent with this, but the results of Rodbard (1) who found that breath-holding times on oxygen at 28,000 feet were less than at ground level on air can not be explained on this basis.

The changes in the R.Q. and the sequence of the changes in alveolar composition during breath holding are shown in figure 2, which represents data on three subjects breathing air. Starting with an alveolar air represented by the region of the curve marked 'normal', the breath was held for various periods of time, after which the alveolar air was exhaled and analyzed. The alveolar point moves up the 'breath-holding curve' and gradually approaches the breaking point line.

In the other direction the line can be extended from the normal region to lower pCO_2 values by voluntary hyperventilation for different periods at a high rate. In this way the alveolar air changes so as to approach the point on the axis of abscissae from which the R.Q. lines radiate (8). This point represents the composition of the inspired air and can be reached only by an infinite ventilation rate. According to the chart, the R.Q. increases during hyperventilation. Thus the R.Q. is 1.4 where the hyperventilation curve intersects the 1.4 diagonal. When the breath is held the R.Q. becomes progressively less. In this case, however, the numerical magnitude of the R.Q. is not given by the diagonal R.Q. lines, because the original inspired air point can no longer apply when the glottis is closed, but rather by the slope (approximately) of the breath-holding curve. At the beginning of apnoea the slope of this curve is such that $\frac{\Delta pCO_2}{\Delta pO_2} = 0.5$. Since the pN_2 is fairly large in this case the total volume of the lung does not change much so that without serious error $\frac{\Delta pCO_2}{\Delta pO_2} = R.Q.$ The mean R.Q. during the

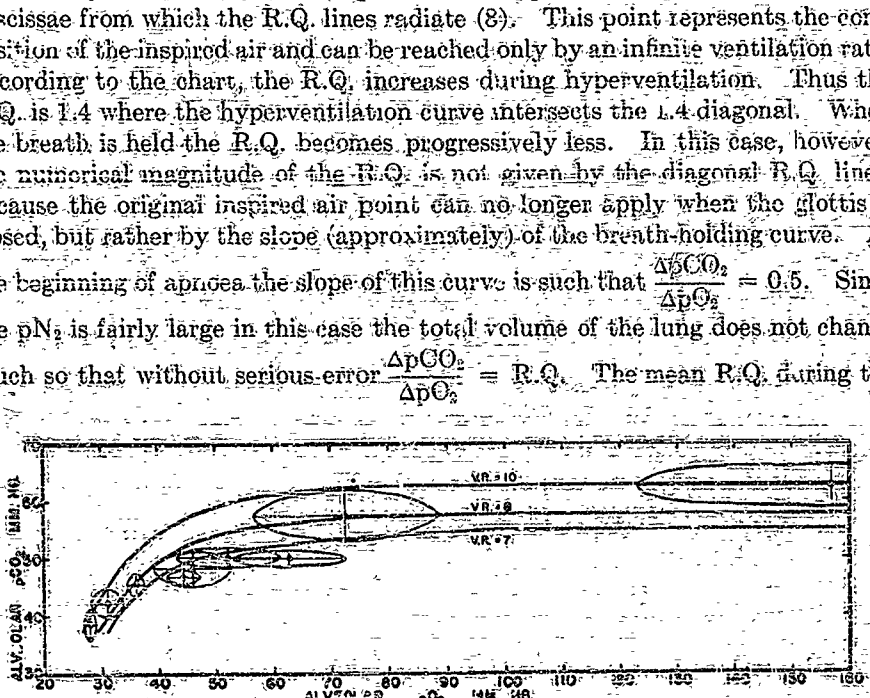


FIG. 3. THEORETICAL BREAKING POINT CURVES constructed as described in the text. The points are plotted from the experimental data in table 1. The standard deviation of each point is indicated by an ellipse.

whole period of apnoea is of course much less. Where the breath-holding curve crosses the R.Q. = 0.5 diagonal, the slope of the curve actually indicates an R.Q. of 0.15. The correct method of calculating the R.Q. from the slope of the breath-holding curve will be given below. (See equations 6 and 7.)

DISCUSSION

For a more quantitative discussion of these results the following symbols will be used:

Let pO, pC and pN be alveolar tensions of O_2, CO_2 and N_2 before breath holding.

p'O, p'C and p'N = similar tensions at the breaking point

FC and F'C = the fraction of CO_2 in the lungs before breath holding and at the breaking point, respectively

V and V' = lung volumes in cc. BTPS before and after breath holding.

x and y = cc. of O_2 lost and CO_2 added, respectively, during breath holding at BTPS.

B = ambient pressure in mm Hg
t = breath-holding time in minutes
X_o = cc. O_2 diffusing out of lung per min. at S.T.P.
Q = normal alveolar R.Q. preceding breath holding
Q′ = mean alveolar respiratory quotient during time t
W = an unknown virtual volume of body water

α = slope of the CO_2 dissociation curve for W. $\alpha = \frac{3500 \text{ cc. } CO_2 \text{ (S.T.P.)}}{\text{liter/atm.}}$

Calculation of alveolar oxygen consumption during breath holding

$$x = \frac{pOV - p'OV'}{B - 47} \tag{1}$$

$$X_o = \frac{pOV - p'OV'}{(B - 47)t} \times \frac{273}{310} \times \frac{B - 47}{760}$$

$$= \frac{pOV - p'OV'}{863t} \tag{2}$$

"The amount of nitrogen in the lung may be assumed to remain constant during breath holding," so

$$p'NV' = pNV$$

and

$$V' = \frac{pN}{p'N} V \tag{3}$$

Substituting (3) in (2) gives

$$X_o = \frac{\left(pO - p'O \frac{pN}{p'N}\right) V}{863t} \tag{4}$$

The average rates of oxygen consumption have been calculated for the breath-holding periods according to equation 4 by assuming an initial lung volume of 3000 cc. and the results are given in table 1. No value is given for experiment 10, because no nitrogen was present and equation 4 does not apply. Equation 2 could have been used in this case had the change in lung volume been known. It is apparent that the rate of oxygen consumption decreases from a normal value of 300 cc/min. during 106 seconds of breath holding at high oxygen tensions to 73 cc/min. for the 23-second period at 18,000 feet. A decrease in the intake of O_2 from the lungs indicates either that the metabolic rate is decreasing or that the O_2 reserves in the body (chiefly blood HbO_2) are being drawn upon. That the latter is more probable is indicated by the following argument.

[3] We have calculated that in the experiments which involve the greatest change in pN_2 (columns 8 and 9 of table 1) the amount of nitrogen taken out of the lung by the blood would be less than 1 per cent of the total nitrogen present.

At 18,000 feet the breath was held for 23 seconds and during that time only 28 cc. of O_2 were removed from the lungs instead of the normal value of about 120 cc. At the same time, however, the arterial saturation fell from a probable value of 70 per cent to an observed value (oximeter) of 18 per cent. If the average fall in all the blood (including venous) were only half as great, at least 10 per cent of the oxygen capacity of the blood or about 100 cc. could have been consumed in the tissues. It may be supposed, therefore, that the O_2 actually used by the tissues does not decrease during the period of breath holding even at anoxic altitudes.

Calculation of the mean alveolar R.Q. during breath holding

$$y = \frac{p'CV' - pCV}{B - 47} \tag{5}$$

$$Q' = \frac{y}{x} = \frac{p'CV' - pCV}{pOV - p'OV'} \tag{6}$$

Substituting (3) in (6)

$$Q' = \frac{p'C - pC\frac{pN}{p'N}}{pO - p'O\frac{pN}{p'N}} \tag{7}$$

Equation 7 has been used to calculate the mean R.Q. during the breath-holding period for all experiments where nitrogen was present. The results are recorded in table 1. At 18,000 and at 16,000 feet the average R.Q. for the period of apnoea is 1.07 and 0.93, respectively, but at ground level on air the value is 0.1 to 0.22 and when extra O_2 is added, values as low at 0.05 result. When the R.Q. is less than unity, there is a decrease in lung volume during the breath-holding period. The lung volume at the end of the breath-holding period may be computed by equation 3. Results of this calculation, assuming an initial lung volume of 3.0 liters, are recorded in table 1. When the breath is held on pure O_2, equations 3 and 7 do not apply, but a relationship between lung volume change and R.Q. is given by equation 6. The final lung volume in experiment 10 has been estimated by the use of this equation, assuming an R.Q. of 0.1 and an initial lung volume of 3.0 liters.

The lung volume is not significantly lowered during breath holding on air at high altitudes, because the R.Q. is about unity, but at ground level and at high oxygen tensions the volume decreases from an initial value of 3.0 liters to a final value of 2.4 liters. Since the breath was held at the end of a normal expiration, this means that the final lung volume is 600 cc. less than the relaxation volume and that some expiratory effort is required to avoid the development of negative pressure within the lungs (11). Breath holding on pure oxygen at high altitudes involves an even greater decrease in volume. We have not investigated this matter thoroughly, but one subject who held his breath on oxygen at 34,000 feet was unable, at the breaking point, to expire enough gas to give a sample for

analysis. It is probable that under such conditions, a decrease to the residual volume might be the decisive factor terminating breath holding.

The high R.Q. values observed during breath holding at anoxic altitudes are the result of the decreased oxygen consumption that occurs under these conditions as described above. The low R.Q. values obtained at ground level where the oxygen consumption remained normal are due to retention of CO_2 in the blood and other tissues, the rising pCO_2 in the lungs creating a less favorable gradient for CO_2 transfer. The amount of CO_2 retained depends on the relative volumes involved of lung air and tissue water, on the slope of the CO_2 dissociation curve of the tissue water and on the length of time available for equilibration.

The total CO_2 (S.T.P.) formed during a period of breath holding is given by

$$(F'CV' - FCV)\left(\frac{B - 47}{760} \times \frac{273}{310}\right) + (F'C - FC)\alpha W \qquad (8)$$

If the alveolar O_2 consumption remains the same as before breath holding,

$$\frac{(F'CV' - FCV)\dfrac{(B - 47)}{(863)}}{(F'CV' - FCV)\dfrac{(B - 47)}{(863)} + (F'C - FC)\alpha W} = \frac{Q'}{Q} \qquad (9)$$

Multiplying by $\dfrac{B - 47}{B - 47}$ to convert F to p gives

$$\frac{(p'CV' - pCV)\dfrac{(B - 47)}{(863)}}{(p'CV' - pCV)\dfrac{(B - 47)}{(863)} + (p'C - pC)\alpha W} = \frac{Q'}{Q} \qquad (10)$$

If values from table 1 for experiment 5, in which the breath was held on air at ground level for 35 seconds, are substituted in this equation, W is found to be 1.57 liters. For experiment 9, in which the breath was held 106 seconds on a higher oxygen mixture, W comes out to be 3.08 liters. The value of 3500 for α is the slope of the CO_2 dissociation curve for blood at 45 mm Hg from Field *et al.* (12). Some justification for using this value for the tissues is found in a paper by Adolph *et al.* (13), who found that for a given rise in CO_2 tension, 3–18 per cent of the CO_2 was absorbed by the blood and 82–97 per cent or about nine times as much, on the average, by the tissues. Since the total volume of body water is about nine times the blood volume, the slope of the CO_2 dissociation curves for blood and tissues must be about equal. If α is taken as only half that of blood, as indicated by the experiments of Shaw (14), the values of W will be doubled, but at any rate these calculations indicate that the CO_2 formed during breath holding equilibrates virtually with only a small fraction of the total 40 or 45 liters of body water. The blood volume alone is ample to account for it.

Actually, of course, the total blood volume is not equilibrated nor is any other tissue. The blood leaving the lungs has a progressively higher pCO_2 as breath holding continues, and the tissues with the best circulation will be most nearly

equilibrated. The more actively metabolizing tissues such as brain and kidney will not only produce more of the CO_2 formed during breath holding but will also retain a larger amount, because of their more rapid circulation. Some tissues may be so slowly circulated that during the shorter periods of breath holding they are not affected at all. For a tissue to retain CO_2 during the breath-holding period the duration must be at least as long as the circulation time from the lungs to that tissue. The steady decrease with time in the value $\frac{\Delta pC}{\Delta pO}$ that occurs when the oxygen uptake from the lungs remains constant during breath holding is due, therefore, to retention of CO_2 in progressively greater fractions of the body water. Presumably if the breath were held long enough to stop all O_2 consumption and CO_2 production, and if the circulation continued long enough, the pCO_2 in the lungs would slowly fall, as the poorly circulated areas of low metabolic rate gradually took up from the lungs their share of the CO_2 formed during the apnoea. A slight fall of alveolar pCO_2 has in fact been observed in obstructive asphyxia by Thompson and Birnbaum (15) and by Grodins *et al.* (16), but in similar experiments on dogs in this laboratory (17) the heart apparently stopped before the fall could be recorded.

The theoretical breaking point. Gray (18) has shown how various stimuli and inhibitions to breathing and their inter-relationships may be expressed in a quantitive fashion. The success with which Gray applied his approach to various respiratory problems suggests the application of his methods to the phenomenon of breath holding.

Breath holding is an example of the voluntary inhibition of an ordinarily involuntary process. It seems reasonable to assume that if one could express inhibition in quantitative units, maximum voluntary inhibition would be a constant value independent of the nature of the opposing stimuli. The breaking point in breath holding might then be considered as the point at which the stimulus to breathe becomes equal to the maximum voluntary inhibition.

The principal stimuli acting during breath holding are probably the pCO_2, the H ion concentration, and the pO_2 of the arterial blood. Gray has shown that the partial effects of each of these stimuli may be computed independently and that the net total stimulus is the algebraic sum of all three. The *chemical ventilation equation* describing this relationship is:

$$V.R. = 0.22H + 0.262\,pCO_2 - 16 + \frac{105}{10^{0.038pO_2}}$$

where $V.R.$ is the ventilation ratio or the ratio of the observed to the normal alveolar ventilation. If the bicarbonate capacity is normal, H and pCO_2 are so related that the above equation is simplified to:

$$V.R. = 0.4\,pCO_2 - 15 + \frac{105}{10^{0.038pO_2}}$$

This equation applies exactly to steady state conditions only. Since no equation of this sort has yet been derived to describe the particular unsteady state

that exists during breath holding, the above equation has been used to estimate the stimulus strength existing at the breaking point for each set of data in table 1. The results of these calculations are shown in table 2. The different values obtained for the total stimulus at the breaking point are hardly constant as would be demanded by an hypothesis of a constant maximum voluntary inhibition. This discrepancy may be due to the inaccuracy previously pointed out of applying a steady state equation to an unsteady state, to a less close approach to equilibrium between alveolar air and arterial blood during breath holding than during normal breathing, (although the close correspondence between our breath-holding curve based on alveolar air values and a similar curve based on arterial

TABLE 2. THE THEORETICAL VENTILATION STIMULUS EXISTING AT THE BREAKING POINT OF BREATH HOLDING

pCO_2	pO_2	$V.R._{H,pCO_2}$	$V.R._{pO_2}$	$V.R._{Total}$
38.6	28.0	0.4	9.1	9.5
42.3	31.1	1.9	6.9	8.8
45.6	36.1	3.3	4.3	7.8
46.9	44.2	3.8	2.2	6.0
50.1	62.7	5.0	0.4	5.4
48.3	45.9	4.3	1.9	6.2
50.2	52.1	5.1	1.1	6.2
57.5	72.5	8.0	0.2	8.2
62.6	157.	10.0	0	10.0
66.5	527.	11.5	0	11.5
Mean				8.0

Explanation of column headings:

pCO_2 and pO_2 refer to the alveolar gas tensions in mm. Hg measured at the breaking point.

$V.R._{HpCO_2} = 0.4pCO_2 - 15$, and is the partial ventilation stimulus due to the H ion, pCO_2 complex.

$V.R._{pO_2} = \frac{105}{10^{0.038pO_2}}$ and is the partial ventilation stimulus due to pO_2.

$V.R._{Total} = V.R._{H,pCO_2} + V.R._{pO_2}$ and is the total stimulus to breathe at the breaking point. According to the proposed hypothesis, it is also equal to the maximum voluntary inhibition.

blood values (6) would seem to minimize this) and possibly to the action of stimuli such as reflexes from the lungs and formation of lactic acid which are not taken into account in the equation. The calculated partial stimulus effects of pCO_2 and of pO_2 in each case are probably relatively correct and indicate that the stimulus at the breaking point in the various experiments of table 1 may be *a*) completely due to high pCO_2, *b*) almost completely due to low pO_2 or *c*) due to various combinations of hypercapnic and hypoxic stimuli. The mean value for the total stimulus at the breaking point (V.R. = 8) has been used as a basis for constructing a theoretical curve for breath holding. By the method indicated in table 3 various pCO_2, pO_2 combinations that should produce a total V.R. = 8 have been calculated. The theoretical breaking point curve for breath holding

has been plotted from these calculated pCO_2, pO_2 combinations on figure 3 (curve labeled V.R. = 8) along with the original experimentally determined points. Two other similarly constructed curves assuming constant stimuli of V.R. = 7 and V.R. = 10, respectively, are shown on the same graph for comparison. These curves are of approximately the proper shape, and except at the higher CO_2 tensions, the fit of the curve for V.R. = 8 is hardly worse than the scatter of the original data, which is indicated by the ellipses of standard deviation surrounding each point.

Although the hypothesis that the breaking point of breath holding occurs when the total stimulus to breathe becomes equal in value to a constant maximum voluntary inhibition is not proven by the above treatment, the results are gratifying enough to suggest further work. For example, the curve for the breaking point should be displaced downwards and to the right in persons acclimatized to

TABLE 3. CALCULATED pCO_2, pO_2 VALUES THAT WILL GIVE A TOTAL VENTILATION RATIO EQUAL TO 8

$V.R._{H,pCO_2}$	$V.R._{pO_2}$	pCO_2	pO_2
8	0	57.5	100
7	1	55.0	83.2
6	2	52.5	45.2
5	3	50.0	40.5
4	4	47.5	37.4
3	5	45.0	34.7
2	6	42.5	32.6
1	7	40.0	31.0
0	8	37.5	29.3

Explanation of column headings:
$V.R._{H,pCO_2}$ refers to the partial stimulus effect assumed due to the H ion, pCO_2 complex.
$V.R._{pO_2} = 8 - V.R._{H,pCO_2}$
pCO_2 was calculated from the equation, $V.R._{H,pCO_2} = 0.4\ pCO_2 - 15$
pO_2 was calculated from the equation $V.R._{pO_2} = \frac{105}{10^{0.038pO_2}}$

altitude because, as Gray has pointed out, the ventilation of such individuals has increased sensitivity to CO_2. Exercise, either active or passive, should also similarly displace the curve because a strong reflex stimulus to breathe would be added to the H, pCO_2, pO_2 combination. The maximum voluntary inhibition estimated above and expressed as V.R. = 8 is close to the maximum ventilation rate attained during active muscular exercise. If a person exercised at a rate such that his ventilation equalled the maximum voluntary inhibition, then he should not be able to stop breathing at all. His breath-holding time would be zero.

SUMMARY

1. Breath holding was investigated in eight subjects at inspired oxygen tensions varying from 69 to 694 mm Hg. The time, HbO_2 per cent, CO_2 and O_2 alveolar tensions were recorded at the breaking point.

2. At high O_2 tensions the breath-holding time was long, the R.Q. was 0.05 to 0.1 due to retention of CO_2 and the rate of O_2 consumption during apnoea was normal.

3. At low O_2 tension (13,000 feet) the breath-holding time was short, the rate of O_2 consumption only about one-fourth the normal, so that the R.Q. was about 1.0.

4. When R.Q. is less than 1.0 the lung volume tends to decrease. If N_2 is present this results chiefly in increasing pN_2 so that pO_2 decreases rapidly. When N_2 is absent the decrease in volume chiefly prevents the pO_2 from falling, so that the pCO_2 is much higher at the breaking point for the same initial alveolar pO_2.

5. Theoretical treatment of the data indicates that the breaking point of breath holding occurs when the sum of the separate partial stimuli from low pO_2 and from high pCO_2 gives a total stimulus sufficient to produce an alveolar ventilation about eight times the normal.

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RESPIRATORY ACCLIMATIZATION STUDIES OF MAN AT 14,200 FEET, MT. EVANS, COLORADO*

by

H. Rahn, H. T. Bahnson†, J. E. Muxworthy, Jr. and J. M. Hagen

Previous studies have indicated that the alveolar air changes which follow continued exposure to altitude can be predicted and that during this course large changes occur which make the respiratory center more sensitive to CO_2.

This study was designed to test these predictions at a higher altitude than previously used and in particular to test the changes in response of the respiratory center by maximum breath holding time on air as well as after breathing oxygen. While the breaking point on air reflects the response to both O_2 lack and CO_2 excess the breaking point on O_2 is only a measure of sensitivity to CO_2 and/or pH (2).

All alveolar air samples were obtained by the method of Haldane by expiring rapidly at the end of a normal expiration. Alveolar samples were also obtained at the end of maximum breath holding time. All samples were analyzed on the Icc Scholander Gas Analyzer. The breath holding was started at the end of a normal expiration and held as long as possible. Breath holding on oxygen was preceded by a five minute ventilation of pure oxygen from a demand regulator. 4 male subjects between the ages of 28 and 37 served in all experiments. Four control values were obtained during 4 days at Rochester, N. Y. on each subject. In addition, the subjects were exposed for at least 30 minutes to a total pressure of 460 mm Hg in a decompression chamber and their normal alveolar air and breath holding values recorded. Four days after the last control value the first tests were made on Mt. Evans and continued for 7 days at a barometric pressure of 460 mm Hg.

RESULTS AND DISCUSSION

The mean values of all 4 subjects are presented in Table 1. During the process of acclimatization the alveolar O_2 gradually rose and the CO_2 fell. The final values at the end of 7 day exposure coincided with the "acclimatized" alveolar air curve for this particular altitude as established in our previous work (1). The R.Q. values calculated from the alveolar O_2 and CO_2 are below normal. A similar observation was made at 10,000 feet (1). These low R.Q. values we feel may arise from an artifact in alveolar air sampling, particularly when the Haldane method is used. As has been pointed out previously (3) this method is apt to yield a low R.Q. because the breath is essentially "held" during the forced expiration.

The breath holding values on air follow closely the changes observed in the normal alveolar air over the 7 day exposure. These two values bear a relationship to each other similar to that observed during acclimatization at 10,000 feet (1).

* These studies were made at the Inter-University High Altitude Laboratory, Mt. Evans, Colorado.

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TABLE 1

Changes in Alveolar Gas Concentrations Before and After Breathing Holding on Air and Oxygen and Breath Holding Times During Acclimatization of 4 Subjects at an Altitude of 14,200 ft.

mm Hg.	Location	Date	Normal Alveolar			Alveolar gas after Breath holding on air			Alveolar gas after Breath holding on O_2	
			pO_2	pCO_2	R.Q.	pO_2	pCO_2	Seconds	pCO_2	Seconds
746	Rochester, N. Y.	8/8-8/11	99.9	39.0	.82	60.1	48.0	44	65.7	213
460	Pressure Chamber	8/9	42.7	37.1	.82	33.6	41.1	25		
461	Mt. Evans	8/15	45.0	32.5	.75	37.2	36.0	22		
461	"	8/16	45.6	32.5	.76	35.9	35.8	20	50.9	180
459	"	8/17	47.7	31.0	.76	39.4	35.8	18		
459	"	8/18	45.2	30.5	.71	38.2	34.2	16	44.9	145
460	"	8/19	45.9	30.9	.72	39.0	33.7	17		
461	"	8/20	48.8	29.7	.76	42.6	33.2	14	44.6	130
460	"	8/21	49.6	29.5	.77	43.2	32.5	16		
460	"	8/22	52.2	28.9	.81	45.9	31.3	15	44.5	126

The breath holding time on air show the typical reduction with time beyond that observed at the acute exposure. Schneider (4) was the first to make this observation and to suggest that this is brought about by a loss of alkali reserve. The present data fit remarkably well the few existing data which were previously assembled (1) (see Fig. 1 of this paper) and show the progressive decline in breath holding time on

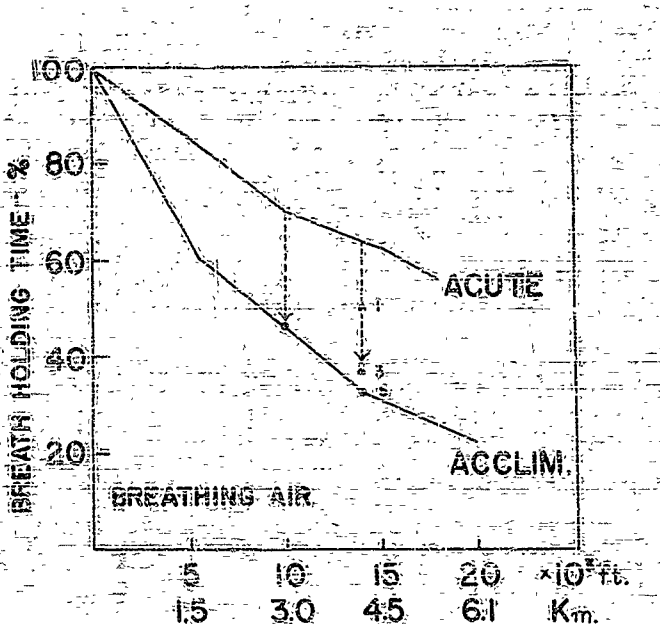

Figure 1

Breath holding time, as percent of values obtained at sea level, plotted against altitude when breathing air. The dotted lines indicate the reduction which occurs with time during acclimatization at 10 and 14,000 feet. The small numbers indicate the days of residency at altitude.

air at this altitude. While the difference between 100% breath holding time and the acute curve represents the effect of the low O_2 tension, the difference between the "acute" and "acclimatized" curve must represent a slow process which increases the sensitivity of the respiratory system with time. That this is not O_2 lack can be shown by breath-holding on pure oxygen when oxygen lack is no longer a factor. Under this condition (Fig. 2) one may likewise observe a reduction in breath holding time. A reduced buffering capacity to CO_2 due to the loss of alkali reserve might be the mechanism involved. The changes in alveolar CO_2 with breath holding on pure oxygen are rather striking. While at Rochester, N. Y. a change of 26 mm pCO_2 was tolerated, this difference was finally reduced to 15 at 14,000 ft., a reduction of 42%. This is almost the same as the reduction in breath holding time. In Table 2 these values are compared with similar observations previously made at

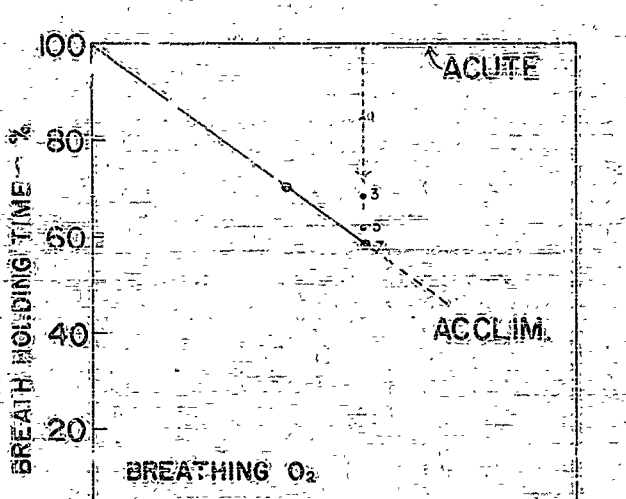

Figure 2

Breath holding time when oxygen is breathed at altitude. Other designations similar to Fig. 1.

10,000 feet. They suggest that the rate at which CO_2 accumulates in the lung and tissues under these conditions is directly proportional to the maximum breath holding time.

In any event, breath holding time on air as well as on oxygen is reduced with acclimatization and this reduction is probably associated with the change in alkali reserve. It serves as a convenient index of the respiratory acclimatization in man.

TABLE 2

Altitude	10,000 ft.	14,000 ft.
% Reduction in B. H. Time on pure oxygen	30	41
% Reduction in ΔpCO_2 during B. Holding on pure oxygen	33	42
% Estimated fall in alkali reserve	18	22

SUMMARY

1. Four subjects were acclimatized for a 7 day period to an altitude of 14,200 ft. on Mt. Evans, Colorado at an average barometric pressure of 460 mm Hg.

2. The alveolar O_2 and CO_2 concentration changed with time in a fashion predicted by a previous study (1).

3. In addition the alveolar air concentration at the end of maximum breath holding time on air and oxygen were obtained.

4. The breath holding times on air as well as oxygen decreased with acclimatization and probably reflect the changes in the alkali reserve. Breath holding time serves as a convenient index to the degree of altitude acclimatization obtained.

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III. BREATH HOLDING STUDIES: EFFECTS OF EXERCISE

by

John F. Muxworthy Jr.

Extensive data on the physiology of maximum breath holding time were established during the war years by various workers. Most of these studies concerned themselves with recording the maximum time that the breath could be held. Engel et al. (1) and Otis et al. (2) respectively studied in addition the arterial blood gas composition and alveolar gas composition at the breaking point. Otis et al. showed that the alveolar gas composition at the breaking point is remarkably constant in all normal individuals tested and thus serves as a convenient index of the sensitivity of the respiratory center. Thus in the following experiments it is assumed that the necessity for the termination of voluntary apnea is equal to a definite ventilation urge and that this in turn is induced by a particular concentration of CO_2 and/or O_2. Therefore, any alteration of the alveolar gas concentrations at the end of a period of maximum apnea under various types of stress serves as a convenient index of any change in the sensitivity of the respiratory center. Thus, it may be likened to the classical test of inhaling CO_2 mixtures and recording the changes in alveolar CO_2 and O_2 which may bring about a given ventilation increment. In this case then, the breaking point is assumed to correspond to a definite and constant ventilation increment. Otis et al. (2) applying the Gray multiple factor theory came to the conclusion that this breaking point of maximum apnea at rest is equal to an alveolar ventilation ratio of about 8.0.

So far only the stress of changes in inspired O_2 concentration have been studied. These studies indicate that CO_2 is the only stimulus which causes the termination of apnea when an alveolar O_2 concentration above 20% is present, while at very high altitudes where the O_2 concentration is low the O_2 becomes the main stimulus. Between these extremes both the O_2 and the CO_2 contribute to the stimulus to breath after maximum voluntary apnea. This is the situation when the breath is held on room air. In the experiments to be described the breath was held while exercising and breathing room air. It has been shown by various workers that during moderate exercise breathing room air that the alveolar pCO_2 is increased while the pO_2 is slightly reduced. Recently Suskind et al (3) have shown that the arterial gas tensions change in a similar manner and thus suggest that the respiratory center becomes very quickly more tolerant to a considerably higher CO_2 tension than during rest. If this interpretation is correct then the breaking point concentration of alveolar gases also should be modified by exercise.

METHOD

The exercise consisted of a step-up test onto a platform 20 cm high at a rate of 20 times per minute. The subject was well rested in a sitting position before the exercise period and after the exercise he would again assume the resting position during recovery. Alveolar air was sampled from a forced expiration delivered at the end of a norinal expiration. This sample was blown into a long rubber hose and

analyzed immediately by the automatic gas meters. The experiments were performed twice on each of the five trained subjects. In the first run the normal alveolar air was sampled. In the second run the breath was held at the end of a normal expiration and maintained until the breaking point was reached at which point the sample was delivered and immediately analyzed. During this breath holding period the exercise was not interupted.

TABLE 1

Alveolar O_2 and CO_2 tensions as they occur normally and after maximum breath holding during rest, exercise and recovery. The difference between the normal and breath holding values represents the stimulus of each gas to achieve the breaking point. Time - minutes after start of exercise. Breath holding time - seconds. Average of Five subjects.

		Rest		Exercise					Recovery		
	Time			1	3	5	7	9	11	14	18
Alv. pCO_2	Normal	38	38	41	42	44	43	43	37	36	36
	Breath Hold.	47	47	51	55	57	58	57	51	49	48
	Difference	9	9	10	13	13	15	14	14	13	12
Alv. pO_2	Normal	101	101	89	93	90	92	92	105	109	105
	Breath Hold.	56	56	40	42	42	42	41	57	55	56
	Difference	45	45	49	51	48	50	51	48	54	49
Max. Breath Holding Time		48	48	21	16	19	20	19	43	56	57

DISCUSSION

The results are found in Table 1. Fig. 1 shows the relationships of alveolar pO_2 to CO_2 of the normal alveolar air during rest (R), exercise (solid line) and recovery (dotted line) as well as the corresponding changes at the breaking point. The numbers indicate the minutes after the onset of exercise.

The normal alveolar tensions describe a typical performance loop described by Rahn and Otis (4). The steady state (points 5, 7, and 9) indicates that during this exercise a 5mm higher pCO_2 is tolerated than during rest. The criticism that this change represents an error of sampling alveolar air during exercise has been largely overcome by the recent studies of Suskind et al (3) who demonstrated that the observed alveolar O_2 and CO_2 changes during exercise were paralled by similar changes in the corresponding arterial tensions. These observations by themselves would strongly suggest a decreased sensitivity of the respiratory system to CO_2.

Such a change in response to CO_2 would allow one to predict that the changes in alveolar O_2 and CO_2 resulting from maximum breath holding would also reflect this

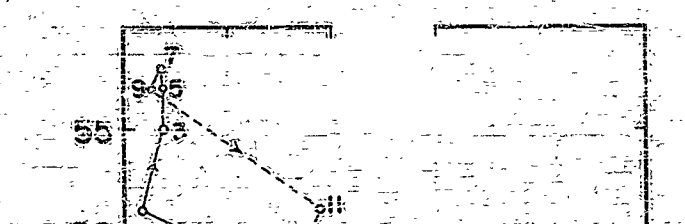

Figure 1

altered response. As the figures in Table 1 indicate one can see that the difference between normal and breaking point CO_2 and O_2 are actually greater during exercise than at rest and Fig. 1 shows a performance loop which is wider in both dimensions, than the normal alveolar air loop. Thus the breath holding data give additional support for a greater CO_2 tolerance during exercise.

It has been previously shown (4) that this increased CO_2 tolerance during exercise can be increased even more by breathing 100% oxygen instead of air. A few preliminary determinations of the alveolar CO_2 at the breaking point during exercise while breathing 100% oxygen show the rather high concentration of 84 mm Hg (12.0%), while at rest they are about 65 mm Hg (9.5%). These values are of particular interest because they approach the concentrations where CO_2 begins to act as narcotizing agent.

SUMMARY

Measurements of the alveolar pCO_2 and pO_2 as they normally occur and at the end of maximum breath holding were made at rest, during a 10 minute period of exercise and during the recovery period. These data show that during exercise greater changes in CO_2 and O_2 are necessary to induce the breaking point of breath holding and suggest that the sensitivity of the respiratory system to CO_2 is reduced.

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EFFECT OF AMMONIUM CHLORIDE INGESTION UPON BREATH HOLDING

by

Robert C. Stroud

Breath holding can be considered a voluntary inhibition of all the centrogenic and reflexogenic drives which stimulate alveolar ventilation. Therefore, in designing the experiment described in this paper, it was felt that an analysis of the arterial pH, Pc and Po values obtained at the breaking point of breath holding under various predetermined conditions, along with a measured change in the plasma CO_2 dissociation curve, should offer a means of some quantitative evaluation of the factors involved in the respiratory drive.

EXPERIMENTAL METHOD

Each of six male subjects between the ages of twenty and thirty years underwent the following procedures: for a series of three or more days one resting alveolar air sample, one alveolar air sample at the breaking point of breath holding and one alveolar air sample at the breaking point following the breathing of pure oxygen were obtained. All alveolar samples were end expiratory and obtained in the sitting position. Each sample was analyzed for CO_2 and O_2 by means of the gas analyzer described by Scholander (1943). 10 ml. of venous blood were drawn from the subject within 15 minutes of the time the samples were delivered. The carbon dioxide capacity of the true plasma, from fully oxygenated blood at two different CO_2 tensions, was determined. Thus it was possible to represent the CO_2 dissociation curve for each blood sample using a log-log plot.

After establishing base-line values the subject began ingestion of 15 grams of ammonium chloride per day for three days. The salt was dispensed in 0.5 gram enteric coated tablets. Ten of these tablets were ingested after each meal.

Three similar alveolar air samples were taken as close as possible to one and one half hours after the ingestion of 15, 30 and 45 grams of ammonium chloride. Following the ingestion of 45 grams of ammonium chloride on the third day, another 10 ml. of blood was drawn and analyzed for plasma bicarbonate level. Finally, on each of the following four to six days one resting alveolar sample was obtained and analyzed in an effort to determine the pathway of recovery from ammonium chloride acidosis.

By means of the data obtained it was possible to calculate the arterial plasma pH both under resting conditions and at the breaking point of breath holding following the breathing of pure oxygen. In order to calculate the pH at the breaking point following the breathing of room air, it was necessary to correct for the unsaturation of the blood. This was done by using the nomogram of A.V.B.'s blood relating arterial Pc, Po and $(CO_2)_s$ as presented by Henderson (1928), and assuming an alveolar-arterial oxygen gradient of 8 mm.

In order to represent the data under uniform conditions, all resting alveolar samples were 'corrected' to a barometric pressure of 749 mm. of Hg, assuming that the alveolar Pc and R would remain constant but the Po would vary in accordance with the relationship expressed by the alveolar gas equation.

$$R = \frac{.791\ Pc}{.209\ (B - 47 - Pc) - Po}$$

and where B = the barometric pressure at the time the sample was taken.

RESULTS

Table 1 summarizes the changes in alveolar gas tensions due to acidosis and to breath holding.

TABLE 1

Alveolar Sample Summary
Weighted Averages

State	Resting P_{CO_2} mm. Hg	Resting P_{O_2} mm. Hg	Alveolar R	B.H.A. P_{CO_2} mm. Hg	B.H.A. P_{O_2} mm Hg	B.H.T. sec.	B.H.O. P_{CO_2} mm. Hg	B.H.T. sec.
Normal	38.7	100.7	.82	48.0	61.1	53	64.0	205
SD	1.3	2.1		2.2	8.5	10.3	4.6	24
15g. NH_4Cl	36.1	102.8	.79	44.3	61.9	45	58.6	165
SD	0.6	1.5		1.6	19.7	9.7	3.6	49.4
30g. NH_4Cl	33.8	108.5	.85	42.5	72.3	39	58.7	151
SD	2.7	5.9		4.1	12.3	6.4	5.1	40.8
45g. NH_4Cl	31.6	110.4	.84	41.5	66.7	44	56.7	146
SD	1.5	4.5		2.6	13.4	21.3	4.6	34.5
1 day rec.*	34.1	104.0	.73					
SD	1.3	1.4						
2 day rec.*	38.2	100.5	.79					
SD	0.9	4.2						
3 day rec.*	40.2	94.0	.75					
SD	2.1	6.1						
4 day rec.*	40.7	98.0	.81					
SD	1.3	1.4						
5 day rec.*	38.6	105.3	.92					

BHA – Breath holding following the breathing of room air
BHT – Breath holding time
BHO – Breath holding following the breathing of 100% oxygen
SD – Standard deviation
* recovery

Table 2 summarizes the calculated (CO_2)s and plasma pH changes during breath holding for both the normal and acidotic subjects.

Figure 1 represents the average CO_2 dissociation curves obtained before and after ingestion of 45 grams of amonium chloride as well as the alveolar CO_2 at rest and at the breaking points.

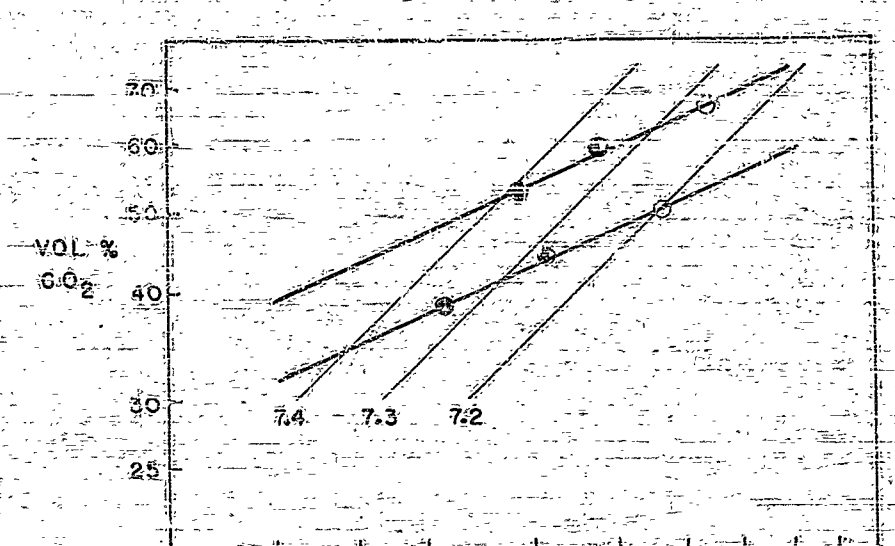

Figure 1

Average Plasma CO_2 Dissociation Curves Obtained Before and After Ingestion of 45 grams of Ammonium Chloride.

The upper curve represents that of the normal subjects while the lower curve represents that of the acidotic subjects, including the isopleths for pH 7.4, 7.3 and 7.2.

The solid circles represent resting arterial values, the half filled circles the breaking point on room air and the plain circles the breaking point on oxygen.

pC indicates plasma pCO_2.

Vol. % CO_2 indicates total volume percent CO_2 content of true plasma.

TABLE 2

Calculated Blood Changes During Breath Holding

State	Subject	Resting $(CO_2)s$ Vol. %	Resting pH	B.H.A. $(CO_2)s$ Vol. %	B.H.A. pH	B.H.O. $(CO_2)s$ Vol. %	B.H.O. pH
Normal	AD	53.7	7.39	64.0	7.35	15.8	7.28
	WD	52.3	7.39	57.8	7.35	67.8	7.26
	AB	54.9	7.39	58.5	7.34	62.8	7.26
	HB	53.6	7.37	57.8	7.33	65.9	7.22
	BR	52.4	7.40	50.2	7.35	-	-
	DF	52.5	7.40	60.2	7.34	64.7	7.28
	Average	53.2	7.39	58.1	7.33	67.2	7.27
45 grams NH_4Cl	AD	37.9	7.31	45.5	7.26	51.3	7.18
	WD	36.2	7.33	42.0	7.25	47.7	7.15
	AB	38.6	7.34	42.5	7.28	47.6	7.22
	HB	41.2	7.33	43.1	7.30	50.6	7.15
	BR	37.2	7.34	42.4	7.26	-	-
	DF	40.3	7.35	48.0	7.28	52.1	7.22
	Average	38.6	7.33	43.9	7.27	49.9	7.18

B.H.A. = Breath holding following the breathing of room air.

B.H.O. = Breath holding following the breathing of 100% oxygen.

DISCUSSION

The ingestion of NH_4Cl produced a 20% fall in the alkali reserve which was partially compensated by a fall in alveolar CO_2. Although breath holding time was reduced by the acidosis the alveolar CO_2 differences (between rest and the breaking point) were the same as before. This is in contrast to findings after altitude acclimatization (3) where a similar reduction in alkali reserve and breath holding time is observed yet the alveolar CO_2 differences are very much smaller. An explanation is sought for the difference in respiratory acclimatization to a lowered alkali reserve when approached from a metabolic acidosis pathway (ammonium chloride ingestion) and a respiratory alkalosis pathway (altitude acclimatization).

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Daily Variations of Vital Capacity, Residual Air, and Expiratory Reserve including a Study of the Residual Air Method

HERMANN RAHN, WALLACE O. FENN AND ARTHUR B. OTIS,

THE PURPOSE OF THESE EXPERIMENTS was to determine the daily variation to be expected in the measurement of the vital capacity and the residual air in a single individual from day to day. No such data were found in the literature with the exception of those given for vital capacity by Griffith *et al.* (1) on 6 subjects extending over a period of a year or more. The data agreed with ours in showing the same standard deviation of the vital capacity and an absence of seasonal variation.

Vital Capacity. Daily values, except on Sundays, were obtained on 12 men and 5 women over a period of 2 to 3 months from September to December. Subjects were always seated and the determinations were made between 4 and 5 o'clock in the afternoon. The highest value of 3 trials was recorded as vital capacity. The spirometer temperature and the barometric pressure were recorded and the volumes were expressed at body temperature, pressure, saturated (B.T.P.S.).

The average results are recorded in table 1. The average vital capacities of all the individuals examined range from 3231 to 6293 cc. with standard deviations ranging from 59 to 193 cc. The average of all the standard deviations is 111 cc. which is 2.36 per cent of the average vital capacity of 4720 cc.

In 5 male subjects the vital capacity was also determined in the morning between 9 and 10 o'clock on about 35 different days, over a period of about 2 months. A comparison of these values with the afternoon values indicates no significant difference in either volume or standard deviation (table 2).

Residual Air. These measurements were carried out 5 times a week for 7 weeks on 5 male subjects by a modification of the method of Lundsgaard and Van Slyke (2). The details of this procedure are discussed below. These values were obtained between 9 and 11 o'clock in the morning with the subject

in a seated position. At the same time the vital capacity and expiratory reserve[2] were measured. The averages of the figures obtained in these measurements are given in table 3 together with the standard deviations. The coefficient of variation of the residual air measurement is nearly three times that for the vital capacity on the same people. The average residual air volume in the sitting position is 30 per cent of the vital capacity and 23 per cent of the total capacity.

TABLE 1. MEAN VITAL CAPACITIES IN 17 SUBJECTS

SUBJECT	DAYS	VITAL CAP.	S. D.	SUBJECT	DAYS	VITAL CAP.	S. D.
		cc.	cc.			cc.	cc.
1	18	5684	142	10	73	5231	95
2	71	6293	141	11	62	4677	193
3	80	4683	92	12	72	4762	109
4	74	4978	59	13	42	2273	74
5	81	4769	77	14	52	4332	85
6	82	5557	154	15	62	3597	178
7	74	4782	90	16	64	3648	66
8	46	5124	88	17	58	3957	145
9	74	5403	90				
				Average		4720	111

All subjects were males except numbers 13–17.

TABLE 2. VITAL CAPACITIES IN A.M. AND P.M. COMPARED

SUBJECT	N	V. CAP. A. M.	S. D.	V. CAP. P. M.	S. D.
		cc.	cc.	cc.	cc.
R. S.	34	4800	72	4773	69
H. R.	35	6260	138	8300	140
H. M.	38	4980	75	4980	89
W. L.	36	5270	121	5250	73
J. H.	35	4110	70	4059	91
Average		5084	95	5070	92

All values in cc., B.T.P.S. N = no. of days on which observations were made.

Effect of Environment. These studies were begun in August and carried on to the end of November 1945. No subjects exhibited any seasonal change during this relatively brief period but simply varied around the mean. The room temperature, humidity and effective temperature as well as barometric pressure were recorded every day. None of these factors showed any correlation with the lung volume fluctuation except the dry bulb temperature. In 5 individuals the vital capacity increased on the average 170 ml. between

[2] Expiratory reserve includes all the air which can be expelled by forcible expiration beginning at the end of a normal expiration.

20° and 30°C. One subject was excluded from this series due to his periodic attacks of asthma resulting in large fluctuations of his vital capacity. It is of interest to note that these fluctuations occurred without change in his total capacity. This is shown by the grouping of points around the negative slope of 1.0 when his vital capacity is plotted against his residual air volume (fig. 1).

Residual Air Method. A modification of the Lundsgaard-Van Slyke (2) method for the determination of residual air was evolved after a long series of preliminary studies on the same subjects eventually used for the daily test. The subject breathed air through a metal three-way stopcock which had a dead space of 40 cc. This value was later subtracted from the residual air volume. After a complete, forced expiration, the subject was connected by a turn of the stopcock to a spirometer containing 2040 cc. of 10 per cent oxygen.

TABLE 3. REPEATED DETERMINATIONS OF RESIDUAL AIR, EXPIRATORY RESERVE AND VITAL CAPACITIES OF 5 SUBJECTS

SUBJECT	DAYS	RESIDUAL AIR		EXP. RESERVE		VITAL CAP.		TOTAL CAP.	
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
R. S.	35	1380	57	2125	100	4800	72	6105	93
E. K.	36	2126	94	2512	169	6258	138	8371	187
H. M.	37	1440	78	1242	134	4975	75	6415	128
W. L.	37	1653	101	2087	142	5270	121	6920	138
T. H.	37	1074	90	903	146	5100	70	5188	125
Average		1536	84	1775	140	5684	93	6614	130

All volumes and standard deviations in cc., B.T.P.S.

The dead space of the spirometer plus the tube connecting the spirometer and the stopcock were also filled with O_2 and had a volume of 460 cc. The subject then inhaled and exhaled the full contents of the spirometer (2040 cc.) once every 3 seconds by watching a clock. At the end of the third expiration an alveolar sample was drawn for analysis and the volume of the residual air was calculated from the percentage of nitrogen which was found. Duplicate gas analyses were made with a Fry analyzer, and any readings that differed by more than 0.2 per cent were discarded. No greater accuracy is required for lung volume determination.

The calculations of the residual air are made as follows:

Let fN and f'N = fractions of N_2 in the alveolar air before and after mixing respectively; V_R = volume of the residual air in ml. B.T.P.S.; V_s = volume of the spirometer and dead space (2,500 ml.) in ml. at room temperature and pressure, saturated; B = atmospheric pressure at time of the test; t = temperature in the spirometer; pH_2O = vapor pressure in the spirometer, 40 = dead space in stopcock in ml.

$$\text{Then} \qquad V_R = V_s \frac{f'N}{fN - f'N} \times \frac{B - pH_2O}{B - 47} \times \frac{310}{273 + t} - 40 \qquad (1)$$

The modification of the method consists in *1*) assuming 80 per cent instead of 79.1 per cent for the nitrogen content of the normal alveolar air prior to the inhalation of O_2, and *2*) in analyzing the mixture after the third rebreathing rather than the fourth or fifth as originally advocated. The reasons for these changes are explained below.

Hundreds of determinations in this laboratory have shown that the average alveolar R.Q. when determined by a forced expiration at the end of a normal expiration during rest in the sitting position is 0.80. With an alveolar pCO_2 of 40 mm. this would mean that the nitrogen percentage is about 80.0 just prior to mixing with the pure oxygen. A value of 79.1 per cent can be obtained only if the alveolar R.Q. is unity. An error of 1 per cent in this value for FN is equivalent approximately to an error of 40 cc. in the final residual air volume.

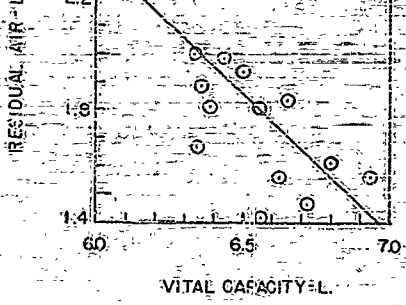

Fig. 1. Exceptional data on one subject, M.E., who was subject to asthmatic attacks. When his vital capacity decreased his residual air volume increased an equal amount.

The formula (*equation 1*) for the calculation of the residual air is based upon the assumption that the amount of nitrogen in the lung-spirometer system does not change during the mixing. On account of the suddenly lowered nitrogen tension in the lung, from 80 per cent to 30 per cent, this is not strictly true, but the error is smaller than the error of the nitrogen analysis. The amount of nitrogen which could enter the lungs under these conditions can be calculated by assuming a cardiac output of 5 l/min. and a lung-blood nitrogen gradient of about 350 mm. Hg (i.e. (80% − 30%) × 700) and an absorption coefficient of nitrogen in blood of 0.011. Thus, in 10 seconds (3 breaths) $\frac{5000}{6}$ cc. × 0.011 or 4.2 cc. of nitrogen would come into the lungs under the most favorable conditions. This represents about 0.1 per cent increase of nitrogen in a lung-spirometer volume of 4000 cc. We have made no correction for this small error.

While this correction for diffused nitrogen can safely be neglected, the change in volume due to the consumption of oxygen and the output of CO_2 is

more important. Immediately after mixing the alveolar and spirometer air, the pCO_2 is reduced to less than half the normal value so that CO_2 pours into the lung rapidly from the blood. Thus, the R.Q. must be well above unity in the first few seconds after mixing starts but rapidly diminishes to abnormally low values owing to the large storage capacity of the body. It will be shown, however, that for the period of the first 3 breaths the average R.Q. is nearly 1.0 so that at this particular point the volume change is negligible.

The quantitative aspects of this problem were investigated by analysing alveolar samples (1 cc. each) from successive breaths for nitrogen. The figures

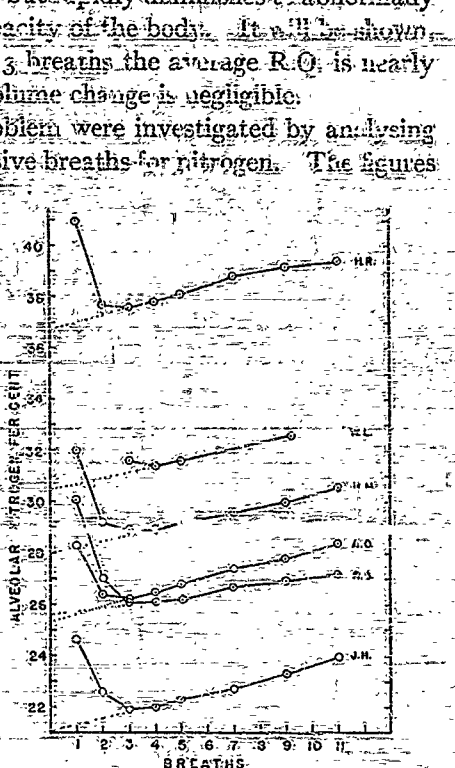

Fig. 2. Alveolar nitrogen percentages during mixing with inhaled oxygen in 6 subjects. Each curve is the average of three separate experiments.

obtained on 6 different subjects for nitrogen are plotted in figure 2. Each point represents the average of 3 separate trials. In every case the nitrogen percentage drops from a normal value of 80 per cent to 20 or 30 per cent as a result of the inhalation of oxygen. A minimum value is reached at about the third breath when the mixing may be regarded as practically complete. After this the nitrogen percentage slowly increases. This slow increase is too great to be accounted for by the elimination of nitrogen from the blood but is due rather to the decrease in volume of the lung-spirometer system due to the absorption of oxygen with a very small CO_2 output.[3] It is tempting to extrapolate this slowly rising curve to zero time and to take the extrapolated nitrogen percentage for the calculation of the residual air. This would presumably be correct if the R.Q. remained constant during the rebreathing but this is not the case. During the early stages of the rebreathing the CO_2 tension is much

[3] A similar low R.Q. is found during breath holding which we have discussed elsewhere (13).

below normal and CO_2 must be coming off into the lungs at a very high rate. The volume of the lung spirometer system must therefore be actually increasing rather than decreasing during the first few breaths. To calculate the residual air, therefore, it is necessary to find the nitrogen percentage for a theoretical instantaneous mixing of the lung and spirometer air or, in other words, the nitrogen percentage which prevails at a time when the volume of the system is the same as it was at the beginning of the rebreathing. When the volume is the same the average R.Q. from the beginning will necessarily be equal to 1.0.

It might at first be supposed that the minimum of the nitrogen curves in figure 2 represents the time when the R.Q. is changing from values above 1 to values below 1. This is not necessarily the case however because the initial fall in the nitrogen percentage is largely due to the progress of the mixing process which overshadows the volume changes.

The theoretical speed of attainment of homogeneity can be calculated from the volume of the residual air, the dead space connecting the lungs with the stopcock and the spirometer and the volume of the spirometer which was assumed to be emptied at each breath. It is assumed that there is no gas exchange in the lungs and complete mixing in the alveoli. With 80 per cent nitrogen in the lungs to begin with and 0 per cent in the spirometer (pure oxygen) the values for the nitrogen percentage in the spirometer and the lungs respectively after the first three expirations were calculated as shown in table 4.

This calculation partially justifies the use of the third expiration for the calculation of the theoretical percentages for instantaneous mixing from equation 8 and confirms some similar calculations from rebreathing experiments on models by Rauwerda (3).

In order to investigate the changes in the R.Q. during different phases of the rebreathing period we have studied two subjects in greater detail, analyzing consecutive breaths for CO_2 and O_2 as well as nitrogen. The figures are given in table 5 and are plotted in figure 3. The oxygen percentage increases rapidly until about the third breath and then diminishes at a more or less linear rate as determined by the rate of oxygen consumption of the body and the volume of the gas. Conversely the CO_2 percentage diminishes rapidly at the first breath and then increases at first very rapidly and then more slowly. The striking fact is that the CO_2 does not diminish as much as would be expected from the dilution of the nitrogen. This is shown by the two lowest curves in figure 3 calculated by the expression $\frac{5.3\,fN}{80}$ where 5.3 is the assumed initial alveolar CO_2 percentage and fN is the fraction of nitrogen found in the alveolar sample taken at the breath in question. This calculated curve represents the concentration of CO_2 which would have obtained had there been no CO_2 output whatever during the experimental period and the interval be-

tween this curve and the observed curve represents, therefore, the actual rate of CO_2 output; this rate is high at first but soon approaches a plateau. These rates are slightly exaggerated during the first two breaths because at that time the mixing is not quite complete between the alveoli and the spirometer and the CO_2 percentage is slightly higher in the lung fraction. The dotted lines

TABLE 4. COMPLETENESS OF MIXING AFTER THE THIRD BREATH

EXPIRATIONS	NITROGEN PERCENTAGE	
	SPIROMETER	LUNGS
0	80.6	0
1	26.6	34.4
2	31.9	33.4
3	33.2	33.3

TABLE 5. CHANGES IN THE COMPOSITION OF THE ALVEOLAR AIR IN TWO SUBJECTS DURING REBREATHING

NO. OF BREATHS	SUBJECT 1					SUBJECT 2				
	O_2	CO_2	N_2	O_2	CO_2	O_2	CO_2	N_2	O_2	CO_2
	per cent			*cc/min.*		*per cent*			*cc/min.*	
0	68.38	1.92	29.65			59.11	2.54	38.35		
1	63.73	3.5	32.7		1300	52.27	4.33	43.5		1180
2	65.59	4.41	30.0		699	50.57	4.72	39		1293
3	65.64	4.86	29.5	644	431	56.36	5.54	38.3	898	865
4	65.30	5.25	29.4		317	55.45	5.85	38.7		249
5	64.75	5.65	29.6	423	309	54.90	6.00	39.1	1280	85
7	63.73	6.17	30.1	274	171	53.90	6.40	39.7	893	159
9	63.04	6.61	30.4	542	150	53.09	6.72	40.2	721	119
11	62.30	6.80	30.9	708	33					

Volumes of lung spirometer system for calculation of rate of gas exchange were 4065 and 4970 cc. respectively for subjects 1 and 2. Corresponding residual air volumes were 1565 and 2470 cc. The expiratory reserve and total dead space were taken as 2000 and 500 cc. for both subjects. Each figure for O_2 intake or CO_2 output refers to the preceding interval. A blank indicates that the rate for this interval was included in the figure for the next interval. Thus in subject No. 2 the CO_2 output for the 0–1 interval was 1180 cc/min. and the O_2 intake for the 0–3 interval was 898 cc/min. Each breath lasted 3 seconds. The rates of O_2 and CO_2 exchange were calculated from the expression $\frac{V}{t}\left(f'O - f''O\,\frac{f'N}{f''N}\right)$ where f' and f'' refer to the breaths before and after the time interval, t. The rates were so calculated according to *equation 8* as to make the rates of oxygen consumption identical in intervals 0 to 3 and 3 to 7.

are extrapolations for oxygen and CO_2 to the points of theoretical instantaneous mixing. The method of calculating these points will be given below.

As was stated previously the extrapolated nitrogen percentage in figure 2 is too low for the calculation of the residual air and it is necessary to obtain the nitrogen percentage at the time of instantaneous mixing. One method of doing this was used by Rauwerda (3). He made measurements of the initial and final volume of the system by terminating as well as beginning

the experiment with a maximal expiration. From the change in this expired volume and a rough estimate of the total volume of the system he was able to correct his final nitrogen value obtained after the [illegible] breath to find the correct value at the initiation of the mixing period. We have chosen a different method based upon the assumption that the oxygen consumption

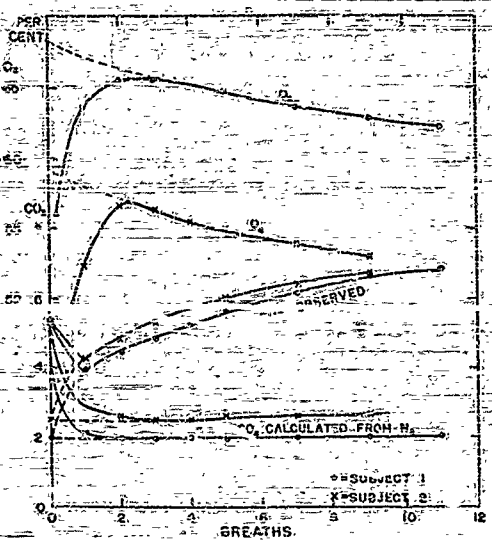

Fig. 3. Changes in the alveolar gas composition of two subjects while rebreathing in the determination of the residual air volume.

remains constant during the period of rebreathing. The method of calculating this is given below.

Let f = the fraction of a gas in the alveoli before mixing; f′ = the fraction calculated after an instantaneous mixing with spirometer air; f″ = the fraction after the third breath; f‴ = the fraction after a later breath; t_1 = the time in minutes between the f′ and f″ sample; t_2 = the time in minutes between the f″ and f‴ sample; V, V′, V″, and V‴ = the volumes (in ml. B.T.P.S.) of the lung-spirometer system at times corresponding to f, f′, f″, and f‴ (V = residual air only); X = cc. of O_2 (B.T.P.S.) lost from lung per minute; N, C, and O = nitrogen, carbon dioxide and oxygen respectively. Assuming that X is the same during the two time intervals, t_1 and t_2,

$$X = \frac{f'OV' - f''OV''}{t_1} = \frac{f''OV'' - f'''OV'''}{t_2} \qquad (2)$$

Assuming that the nitrogen in the lung-spirometer system is constant

$$fNV = f'NV' = f''NV'' = f'''NV''' \qquad (3)$$

Substituting in (2) values of V′, V‴, and V‴ from (3)

$$\frac{f'O\frac{fNV}{f'N} - f''O\frac{fNV}{f''N}}{t_1} = \frac{f''O\frac{fNV}{f''N} - f'''O\frac{fNV}{f'''N}}{t_2} = X \qquad (4)$$

or
$$f'O = f'N\left(\frac{t_1 + t_2 f''O}{t_2 f''N} - \frac{t_1 f'''O}{t_2 f'''N}\right) \quad (5)$$

But
$$f'O + f'C + f'N = 1.0 \quad \text{And} \quad f'C = \frac{fC\,f'N}{fN} \quad (6)$$

Then
$$f'O = 1 - f'N - \frac{fC\,f'N}{fN} \quad (7)$$

Equating (7) and (5) and rearranging

$$1 = f'N\left(1 + \frac{fC}{fN} + \frac{t_1 + t_2 f'O}{t_2 f'N} - \frac{t_1 f'''O}{t_2 f'''N}\right) \quad (8)$$

In table 5 are given all the values of fO, fC and fN at different breaths for two subjects as was previously mentioned. The values at breath No. 0 are for instantaneous mixing (i.e., f'O, f'C and f'N calculated as described from *equations 6, 7,* and *8*). The rates of oxygen consumption and CO_2 output were calculated from a modification of *equation 4* for various intervals assuming the lung volumes given under table 5 (see legend).

The most important feature of table 5 is the value of f'N which agrees remarkably closely with the value of f''N or the N_2 percentage after the third breath. Thus as a result of two opposing errors, the third breath value, in these two subjects at least, is almost exactly equal to the theoretical instantaneous dilution value which is needed for the calculation of the residual air. In other words, at the time of the third breath, the decrease in volume resulting from the consumption of O_2 is just equal to the increase from the gain in CO_2. The ideal point for sampling is then the point where the R.Q. for the period from the moment of mixing is equal to 1.0.

Inspection of the calculated rates of O_2 consumption and CO_2 output in table 5 shows *1*) that the rate of O_2 intake is higher than normal but remains apparently constant throughout the experiment; and *2*) that the rate of CO_2 output is much higher than the O_2 intake rate at first (R.Q. = 1.0) and falls to very low values (R.Q. = 0.2) at the end.

The values of f'N and f'O (table 5 breath No. 0) were so calculated as to make the rate of O_2 intake during the first 3 breaths equal to the rate in the next 4 breaths when both are corrected to the same initial lung volume or N_2 percentage by *equation 4*.

The rates of oxygen consumption given in the table however are calculated for each interval separately without this common correction (see legend, table 5). While the figures therefore are not strictly comparable because the nitrogen percentage does change slightly, this correction is nevertheless smaller than the error of timing the breaths and the general constancy of the values is significant and helps to justify the assumption of a constant rate of oxygen consumption during the procedure upon which *equation 8* was based.

The absolute values of these rates of oxygen consumption are also independent of any assumptions made in the calculations and the values found (638 and 965 cc/min.) are over twice the expected normal value of 300 cc. According to Armitage and Arnott (4) the rate of oxygen consumption is increased from 350 to 700 cc/min. by a single deep inspiration due to a suddenly increased circulation through the lungs. Data were not presented to support this conclusion but it might be doubted whether the result is not due to unequal ventilation of different parts of the lungs. When a deep breath is taken some of the air from poorly ventilated alveoli with a low oxygen content might be brought into the mixture and would then simulate an increased oxygen consumption. This may also explain the excessively rapid fall in the concentration of oxygen which occurs during a single deep expiration, an observation which led Krogh and Lindhard (5) to postulate likewise a sudden increase in the rate of oxygen consumption during a single deep breath.

If however the high observed rate of O_2 consumption were due to incomplete mixture in the lungs it would appear only in the first breath and would not continue throughout the period of observation. In our experiments therefore it seems more probable that the cardiac output is increased for the duration of the rebreathing period, which is approximately one circulation time. Christie (6) has brought forward similar evidence of a 90 per cent increase in cardiac output during 20 sec. of hyperventilation and Rauwerda (3) has confirmed this by observations on the rate of uptake of acetylene during rapid rebreathing. After recirculation begins, the rate of oxygen consumption would presumably return to its normal level.

The high initial rate of carbon dioxide output of around 1200 cc/min. (table 5) calls for some discussion. In the first place the average R.Q. during the first three breaths must be nearly 1.0 because the nitrogen percentage at this point is equal to the calculated nitrogen percentage for instantaneous mixing (IN). Immediately after the third breath at least the rate of CO_2 output is definitely less than the rate of oxygen intake. It seems likely therefore that the R.Q. is above 1.0 at the first breath and below 1.0 at the third breath. The reliability of the figures for CO_2 output given in table 5 for the first three breaths is open to some question because the mixing with dead space oxygen was certainly not complete at this time. This incomplete mixing makes any calculations of oxygen consumption totally unreliable during this period and indeed while the oxygen percentage is increasing the calculated rate of oxygen consumption would be negative. The error due to this incomplete mixing would however be some 15 times greater for O_2 than for CO_2. We would discount therefore the exact figures for CO_2 output during this period but nevertheless believe that the initial R.Q. must be greater than 1.0. Since we do not have reliable figures for discussion it is hardly worthwhile to try to account quantitatively for the high figures of some 1200 cc/min. which

are given. It will suffice to mention that such high rates could not be obtained at the observed alveolar CO_2 tensions without assuming that the cardiac output was increased. This lends further support therefore to the hypothesis advanced to explain the high rates of oxygen consumption.

In conclusion, the residual air should be calculated, if possible, from the nitrogen percentage which results from instantaneous mixing. This can be calculated by *equation 8* if the alveolar air from successive breaths is obtained, on the assumption that the rate of O_2 consumption remains constant. In practice, however, it is shown that the nitrogen percentage after the third breath approximates the instantaneous mixing value so that a single sampling after the third breath can be used conveniently to obtain a correct value.

The recommended procedure for the determination of the residual air is therefore as follows: First expire maximally and turn the cock to the spirometer. Inhale pure oxygen from the spirometer emptying it completely, then exhale the same volume. Repeat this three times at 3-second intervals. The third breath is ended by a maximal expiration and the taking of an alveolar sample which is analyzed for nitrogen. This value of f_N is used in *equation 1* for the calculation of the residual air.

This method for residual air is useful for cooperative subjects but could not serve well for patients. For such cases the more prolonged normal-rebreathing periods recommended by Cournand *et al.* (7) or an open circuit method of Darling *et al.* (8) or Bateman (9) is preferable. We have made no attempt to validate this method against other methods such as those already mentioned and those of Van Slyke and Binger (10), Hurtado *et al.* (14), Rohland (11) and Birath (12). Nor would we claim any superiority for this method over certain others. It is a convenient method in our hands and some of the details of the gas exchange which occurs during the rebreathing period seem to us of general interest for respiratory problems.

SUMMARY

Daily measurements were made of the vital capacities of 17 individuals over a 2- to 3-month period. The average of the standard deviations was 2.36 per cent of their vital capacity volume. Daily measurements of the residual air by a nitrogen dilution method on 5 subjects over a period of two months gave an average standard deviation of 5.5 per cent of the residual air volume. The expiratory reserve and the vital capacities of these same individuals had an average standard deviation of 7.0 per cent and 1.6 per cent respectively for their particular volumes.

Reasons for the modification of the Lundsgaard-Van Slyke method for the determination of residual air are discussed. A method of calculating the nitrogen percentage for instantaneous mixing is given and it is shown that this is approximately equal to the nitrogen percentage after the third expira-

tion. The latter value is therefore used in practice for the calculation of the residual air.

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THE VITAL CAPACITY AT REDUCED BAROMETRIC PRESSURE

by

Hermann Rahn and Daniel Hammond

Over the last 75 years a large number of observations have been made which indicate that the vital capacity is markedly diminished when man is subjected to a reduced atmospheric pressure. Usually these changes have been attributed to the lowered oxygen tension and various phenomenon. A brief summary of the findings to date (see Table 1) suggests that we are dealing with a rather large change in lung volume. A reduction, for instance, of 10% of the vital capacity means that one must account for some 400-500 ml of air which can no longer be displaced. This might mean mechanical inability of the breathing mechanism, an enlarged residual air volume at the expense of the vital capacity or enlargement of the pulmonary vessels. Whatever the cause, so far no proof has been offered which would satisfactorily account for such a large volume change.

However, a critical review of the literature reveals that with two exceptions, no corrections were ever applied to the observed spirometer volume. This becomes rather important, particularly at altitude where not only the external temperatures often differ from those observed at sea level but also water vapor occupies a relatively larger volume for any given vapor tension. If a vital capacity, as it exists in the lung at a pressure of 760 mmHg., 37°C. and fully saturated with water vapor, occupies a space of 5.0 liters, it will shrink when blown into a spirometer at 20°C. to 4.6 liters, a reduction of 8%. If this same lung volume of 5 liters is expelled at 18,000 feet altitude (380 mmHg) the 5 liter volume will shrink to 4.35 liters, a reduction of 13% at the identical spirometer temperature. Thus, if no corrections were made, the sea level value of 4.6 would be compared to 4.35 and a difference of 250 cc or a reduction of 5.4% of the vital capacity recorded. The cause for this discrepancy is the water vapor which occupies at one-half atmosphere exactly twice the sea level volume in the spirometer as well as in the lung. Thus, when the water vapor is blown from the lung into the cold spirometer, twice as much will condense at one-half atmosphere. In addition, should the temperature at 380 mmHg be 15°C. instead of 20°C. then the original 5 liter volume would shrink to 4.2 liters and a difference of 400 cc. (4.6-4.2) or a reduction of nearly 9% of the vital capacity would be recorded.

Since the magnitude of such errors approaches the values previously recorded in the literature, it became of interest to reinvestigate the whole problem of the effect of barometric pressure on changes in vital capacity and with the aid of proper corrections, redetermine the magnitude of such changes. Therefore, the vital capacity, and in many instances the expiratory reserve volume, was measured (1) during acute exposure in a low pressure chamber at altitudes simulating 10, 14 and 18 thousand feet breathing air, (2) at ground level breathing oxygen-nitrogen mixtures

TABLE I

A. Acute Exposure to Low Oxygen. (Low pressure chamber or breathing low oxygen mixtures at ground level.)

Author	Pressure	Approx. Altitude	Reduction of V.C.	Remarks
	mmHg.	Ft.	%	
v.Vivenot 1868 (1)	424		14, 10	
Bohr 1907 (2)			none	insignificant increase breathing mixtures of 8 - 12% oxygen
Schneider 1932 (3)		10,000 20,000	none 8	average of 24 subjects
Hurtado et al 1934 (4)	419	16,000	14, 4, 8	3 subjects

B. Prolonged Exposure to High Altitude.

Hewett 1875 (5)	682	3,000	11, 12	return to normal after 3 days
Bert 1878 (6)	440	14,400	50	Monte Rosa
Mosso 1889 (7)	440	14,400	20, 13, 3, 10, 9, 6	Monte Rosa
Schumburg and Zuntz 1896 (8)	626 480	12,000	11, 8 7, 3	
Durig 1911 (9)	440	14,400	16, 15, 14, 16	no change over 3 wks.
Barcroft et al 1923 (10)	460	13,200	13, 2, 4, 3, +1	1 wk. at Cerro de Pasco, Peru
Grollman 1930 (11)		14,100	13	Pike's Peak
Schneider 1932 (3)		14,100	7 - 15	9 subjects; maximum decrease on 1st or 2nd. Pike's Peak
Verzar 1933 (12)	492	11,400	2 - 24	Range of 5 subjects, average 5%. Return toward normal after 2 - 7 days. Jungfraujoch.
Verzar 1945 (13)	492	11,400	9 - 12	Range of 9 subjects. Jungfraujoch.

Only Durig and Barcroft mention that "corrections" were applied to spirometer measurements. The correction factors are not given.

simulating the inspired oxygen pressure of the foregoing experiment, (3) at altitudes of 20, 30 and 40 thousand feet breathing oxygen with and without positive pulmonary pressure breathing, (4) during a 7-day exposure on Mt. Evans, Colorado at an altitude of 14,260 feet, and (5) after artificial distension of the gastro-intestinal tract at ground level.

METHOD

A simple 6 liter spirometer provided with a thermometer in the bell served as the only instrument. All measurements were made sitting upright and bending over during the last part of the expiration was not permitted. All the subjects were [illegible] students and staff members of the department. Of three measurements taken at any one trial, the largest one was used in the final computation unless otherwise noted.

Each spirometer reading was corrected to the volume it would occupy at body temperature, ambient pressure and fully saturated with water vapor, B.T.P.S. This should represent the anatomical volume it would occupy in the body. Thus, the corrected lung volume, $V_{B.T.P.S.}$

$$= V_{obs.} \times \frac{273 + 37}{273 + t} \times \frac{P - P_{H_2O}}{P - 47}$$

where $V_{obs.}$ is the observed spirometer volume, t the spirometer temperature, P the barometric pressure, P_{H_2O} the water vapor tension at the temperature t and 47 the vapor pressure of water at body temperature.

RESULTS

I. Acute exposure to reduced ambient pressure breathing air.

These experiments were carried out on 18 individuals in a low pressure chamber at least two hours after their last meal. After entering the chamber, 20 minutes were allowed for resting and recording the ground level values of the expiratory reserve volume and the vital capacity (average barometer 748 mmHg). The chamber was then evacuated successively to 523, 446, and 379 mmHg pressure corresponding respectively to 10,000, 14,000, and 18,000 feet of the U. S. Standard Atmosphere. Five minutes elapsed during each successive ascent, five minutes were allowed for adjustment to each new pressure and measurements were made during the next five minute period before ascending to the next altitude level. At the end of the trials at 18,000 feet oxygen was administered through an oxygen demand regulator for five minutes followed by additional measurements. Immediately after recompression to ground level, measurements were made again. The entire procedure lasted approximately 1-1/2 hours. After-effects, if present, were limited to headache and fatigue.

All recorded values were first corrected to B.T.P.S. and then expressed as percentage of each subject's vital capacity at ground level. Table 2 shows that at 14 and 18 thousand feet there is an average reduction of 2.4 and 3.8% respectively. The bottom row expresses the probability (P) of obtaining a deviation of this magnitude if the true mean is 100%. From this analysis the observed differences are

TABLE 2

Vital Capacity and Expiratory Reserve Volume Upon Acute Exposure in a Low Pressure Chamber to Simulated Altitude

Altitude x 10^3 Ft.	Vital Capacity					Expiratory Reserve Volume			
	G.L.	10	14	18	18-O_2	G.L.	10	14	18
Subjects	%	%	%	%	%	%	%	%	%
1	100	99.6	92.2	97.4	95.2	23.4	22.6	17.7	24.8
2	100	98.4	98.9	96.6	100.6	25.2	23.8	23.9	22.6
3	100	99.4	95.4	95.6	100.0	18.5	15.7	23.5	21.3
4	100	98.8	92.4	94.8	99.7	21.2	16.9	17.3	16.4
5	100	100.2	100.0	95.7	98.6	26.9	22.5	21.1	22.5
6	100	96.2	98.0	89.1	94.1	22.9	19.6	23.2	19.3
7	100	99.7	100.2	97.6	101.6	33.4	31.0	28.8	28.3
8	100	99.1	96.2	95.4	96.5	30.1	30.4	29.9	28.8
9	100	102.1	99.3	100.0	101.0	25.3	25.2	23.9	26.2
10	100	100.0	100.0	99.8	103.0	36.5	35.2	33.8	35.8
11	100	99.6	99.7	91.4	98.4	37.7	35.1	30.7	33.2
12	100	99.4	96.3	93.9	97.8	27.2	22.8	24.9	25.1
13	100	98.2	99.5	95.2	98.6	32.4	20.9	26.8	32.4
14	100	101.7	100.4	98.3	101.8	37.2	41.1	38.0	42.5
15	100	103.7	97.4	98.2	95.6	31.3	30.7	29.5	26.4
16	100	98.3	95.7	97.4	105.0	36.0	39.4	38.4	35.7
17	100	100.6	100.3	--	99.2	33.9	32.6	31.8	--
18	100	99.3	94.3	--	99.8	43.5	42.8	40.7	--
Mean	100	99.8	97.6	96.2	99.0	30.4	28.4	28.0	27.6
Stand. Error of Mean	--	.39	.64	.73	.73	1.61	1.97	1.64	1.74
P	--	.6	<0.01	<0.01	.2	--	.3	.2	.1

18-O_2 indicates that pure oxygen was administered at 18,000 feet.

TABLE 3

Vital Capacities Upon Acute Exposure to Low Oxygen Mixtures at Ground Level

Inspired O_2 % (dry), P = 748	20.9	14.2	11.8	9.9	20.9
Equivalent Altitude x 10^3 Ft.	G.L.	10	14	18	Recovery
Subject	%	%	%	%	%
19	100	101.9	104.3	102.5	102.5
17	100	96.9	94.1	96.2	100.0
7	100	98.1	100.2	100.2	100.2
3	100	98.4	99.4	100.0	98.2
11	100	101.5	95.7	95.7	100.2
2	100	100.0	100.0	100.8	100.8
12	100	100.0	95.5	97.0	100.2
5	100	97.5	97.8	96.2	99.2
14	100	99.0	97.2	99.3	100.2
Mean	100	99.2	98.2	98.6	100.2
Stand. Error of Mean	--	.58	1.04	.69	.33
P	--	.2	.1	.05	

The mixtures simulated the identical inspired O_2 tensions as in the low pressure chamber run (Table 2) and are for comparison expressed as altitude equivalents. The successive exposures were also of the same duration.

highly significant. When the subjects at 18,000 feet switched from air to oxygen breathing the vital capacity increased again to 99.0, a value which is probably not significantly different from the control at ground level. On the other hand, the difference between the means breathing air and oxygen at 18,000 feet seems to be significant, having a P value of <0.02 and >0.01.

The means of the expiratory reserve volume also show a decrease at higher altitudes, although this trend cannot be considered very significant.

II. Acute exposure to low oxygen-nitrogen mixture at ground level.

In order to evaluate anoxia, per se, without possible side effects of acutely reduced pressure, gas mixtures low in oxygen were administered to 9 subjects who had previously served in the foregoing experiments. Gas was inspired from a tight-fitting face mask connected to a rubber bag reservoir. This bag was fed with nitrogen and air through a dual flowmeter in such a way that the exact time schedule and the same inspired oxygen tensions (moist, at 37°C) as in the foregoing experiment could be duplicated. The inspired gas mixture was continuously analyzed for oxygen with the Pauling oxygen tensimeter and could be controlled to within 1 mmHg oxygen tension. The various inspired gas mixtures are also expressed as altitude equivalents in Table 3.

It may be seen that the mean difference for each altitude equivalent is far less than in the foregoing chamber experiment and, furthermore, that these differences are not very significant. Since the degree and length of anoxic exposure were presumably identical in both experiments, some other factor than anoxia would be necessary to explain the changes observed in the low pressure experiment.

III. Acute exposure to very low pressures breathing oxygen.

In experiment I the pressure as well as the oxygen tension was reduced, while in experiment II only the inspired oxygen tension was lowered. This experiment was designed to lower the pressure as much as possible without reducing the oxygen tension below ground-level values. At 20 and 30 thousand feet simulated altitude breathing oxygen the inspired oxygen tensions are in excess of normal while at 40,000 feet the inspired oxygen tension (B.T.P.S.) is 94 mmHg. and equal to an altitude of approximately 11,000 feet breathing air.

For these measurements, the subject had a large 3-way stopcock inserted in the tube leading from his mask to the oxygen supply demand regulator. The third arm of the stopcock was attached to the 6 liter spirometer. Thus, after a full inspiration or at the end of a normal expiration the cock would be turned and the lung volume was emptied into the spirometer for vital capacity or expiratory reserve volume recording. In an otherwise identical chamber experiment the same four subjects were exposed to a continuous positive pulmonary pressure of 10-15 mmHg supplied from the same demand regulator. During pressure breathing the turning of the 3-way stopcock to the spirometer involved an immediate decrease in pressure and expansion of the gases in the lungs. The volumes measured during pressure breathing were corrected for the pressure in the lungs, i.e., the ambient pressure plus the excess pressure in the lung. In both of these experiments three measurements

TABLE 4

Vital Capacity and Expiratory Reserve Volume at Various Altitudes Breathing Oxygen at Ambient Pressure and at a Positive Pulmonary Pressure of 10-15 mmHg. Average of 4 subjects.

Altitude x 10^3 Feet		Ground Level	20	30	40
Barometric Pressure mmHg.		748	349	226	141
Breathing at Ambient Pressure	Vital Capacity	100.0	101.3	95.7	92.8
	Exp. Reserve Vol.	35.0	31.5	28.9	25.5
With Positive Pressure Breathing	Vital Capacity	100.0	98.9	94.6	97.0
	Exp. Reserve Vol.	67.9	56.4	54.0	52.0

All values are expressed as percent of vital capacity at ground level.

TABLE 5

Vital Capacity Changes During an 8-Day Exposure on Mt. Evans, 14,200 Feet.

		SUBJECTS				AVERAGE of 1st 3 subjects		Spirometer Temperature
		H.R.	E.B.	J.M.	J.H.*	Corrected	Uncorrected	C°
P = 746 - Rochester, N.Y. Average of 4 days as control value		6.33 or 100%	5.95 or 100%	6.13 or 100%	5.55 or 100%	6.14 or 100%	5.79 or 100%	31
P = 634, Denver, Col.,	8/15	102	101	102		102	98	25
P = 460, Mt. Evans,	8/15	99	100	97		99	90	19
"	8/16	98	99	97	105	98	88	17
"	8/17	96	96	96	103	96	88	20
"	8/18	97	100	101	98	99	91	19
"	8/19	104	97	97	97	99	90	17
"	8/20	103	100	101	101	101	93	20
"	8/21	104	101	102	100	102	94	19
"	8/22	104	101	103	96	103	94	17
P = 633, Denver	8/23	100	99	101	100	100	98	27
P = 585, Wyoming	8/29	100	104	105	100	103	92	10
P = 747, "	9/6	101	102	102		102	97	22
P = 744, "	9/7	102	100					19
P = 742, "	9/8	103	101	103		102	96	20

* Previous to his ascent to Mt. Evans subject J.H. was already acclimatized to an altitude of 6000 feet for about 2 months. He had no symptoms of altitude sickness. His control values were obtained after his return to Rochester, N.Y.

were made of the vital capacity as well as the expiratory reserve volume at each altitude on the ascent and again in reverse order on the descent. All the readings, for each altitude, were averaged. The grand average of all four subjects is found in Table 4 where all the values are expressed as percentage of the sea level vital capacity with or without pressure breathing as the case might be.

Both with and without pressure breathing the vital capacities show a decrease at the very low pressures. An even larger change is seen in the expiratory reserve volume. Although the individuals differed in the magnitude of this response it was consistent with all regardless of whether pressure breathing took place or not. The expiratory reserve is, of course, larger under positive pulmonary pressure than without pressure at all altitudes.

The reduction of both vital capacity as well as expiratory reserve volume at these very high altitudes is difficult to explain. At 30,000 feet there is no anoxia with oxygen breathing and at 40,000 feet the anoxia is very slight, indeed. However, the expansion of the abdominal gases is considerable and in many instances the forced expiration into the spirometer became quite painful. It would seem therefore that the expansion of abdominal gases might not only limit the complete inspiration but also expiration and thus account for the reduction in expiratory reserve as well as vital capacity except for the fact that changes in these two entities do not parallel each other.

IV. Chronic exposure to an altitude of 14,200 ft. (P = 460 mmHg.)

During the course of other experiments on Mt. Evans, Colorado the vital capacities of four men were measured daily during their stay of seven days. Control values were established at Rochester, New York for three of the subjects. Three days intervened between the last control value and the first measurement on the summit. There was no particular physical exertion experienced in reaching the laboratory since it is directly accessible by car. The temperature of the hut ranged between 16 and 22°C. However, in these three subjects there was no previous acclimatization to altitude and various degrees of altitude sickness were experienced. These ranged from intermittent attacks of chronic headache to nausea, vomiting and anorexia lasting approximately three days.

Table 5 shows the changes at altitude expressed as percentages of the average control values at Rochester, New York. It may be seen that a 4% reduction occurred in each subject on the third day which was followed by an increase above the Rochester value which was still apparent two weeks later upon return to Rochester, New York. The values of a fourth subject (J.H.), having a different history of altitude acclimatization, are also shown. The uncorrected spirometer values and temperatures are likewise included. The former give an idea of how far they may deviate from the true anatomical volume changes.

V. Effects of artificial abdominal distension upon the vital capacity.

The two previous pressure chamber experiments suggest that the factor of abdominal distension might limit the full inspiration or expiration preceding the delivery of the vital capacity. Blair et al (14) have shown that the normal gas content of the

TABLE 5

Effect of Abdominal Distension Upon Vital Capacity

Abdominal Displacement	700 ml. Fluid and Gas					800 ml. Water	
Subjects	2	11	21	5	12	2	12
	cc	cc	cc	cc	cc	cc	cc
Before Ingestion	4870	5360	5300	4800	4650	5250	5010
After Ingestion	4890	5730	5250	4880	4700	5250	5020

TABLE 7

Effect of Exposure to Low Oxygen Mixtures at Ground Level on the Maximum Expiratory Pressures Developed at Full Inspiration.

Inspired O $_2$ % (dry)	20.9	14.4	12.3	10.4	20.9
Equivalent Altitude x 10^3 Ft.	G.L.	10	14	18	Recovery
Subjects	%	%	%	%	%
19	100	93.6	92.5	88.5	100.5
17	100	75.0	95.7	92.8	87.5
7	100	101.5	88.0	91.0	98.2
3	100	96.6	94.0	89.8	94.0
12	100	92.5	86.4	76.6	87.2
Mean	100	91.7	87.0	83.7	93.2

Values expressed as percentages of pressures measured breathing 20.9% oxygen.

gut is about 1000 ml. During an acute exposure to 18,000 feet altitude such a volume would double, and at 40,000 feet increase 6-7 fold if allowed to expand without resistance. To test the effect of an approximate doubling of the abdominal content at ground level, two subjects swallowed 800 ml. of water, five others drank a bottled beverage whose CO_2 content is standardized at 490 ml. With the added fluid volume this produces an effective displacement of about 700 ml. The vital capacities were tested before and immediately after ingestion and no significant differences were obtained, Table 6. These studies agree with those recently reported by Mills (15).

VI. The effect of low oxygen mixtures upon the strength of the muscles of expiration.

Hartmann (16) showed that the flexor strength of the hand decreased 21% at an altitude of 20,000 feet, and Mosso [cited by Margaria (17)] reported a similar reduction at 15,000 feet. To make tests employing the muscles of respiration, the maximum expiratory pressure was measured breathing various oxygen mixtures. Five subjects were exposed at ground level to the same oxygen concentration and exposure time as in experiment II. With a pipe stem connected to a mercury manometer the maximum expiratory pressure following a full inspiration was measured. The values were recorded as percentages of the pressure obtained breathing 20.9% oxygen, Table 7. In spite of the fact that the recovery values are not in accord with the control values there seems to be definite reduction in the strength of the respiratory muscles employed in this procedure. Certainly the same muscles are employed in the last phase of blowing a vital capacity except they are now maximally shortened instead of being maximally stretched as during the pressure test.

DISCUSSION

The general findings in this study confirm a reduction in vital capacity where man is acutely or chronically exposed to a reduced barometric pressure breathing air. The magnitude of this response, however, is much smaller than previously indicated and is most likely explained by the lack of adequate corrections of the spirometer volume measurements made by previous authors.

Schneider's experiments (3) in the low pressure chamber yielded results similar to ours. There was no significant change at 10,000 feet but an average reduction of 8% at 20,000 feet. When 7 subjects switched at this altitude to pure oxygen the vital capacity was again increased. More difficult to explain are the findings in our second series of experiments. Here the inspired oxygen tension identical to the low pressure chamber runs were achieved by breathing various O_2N_2 mixture at ground level. Statistically, these indicate a barely significant change and suggest the possibility that low oxygen is not an important factor but that the reduction in pressure, per se, has in some way reduced the lung volume in the chamber run. The maximum expansion of intestinal gases at this altitude would yield at best a doubling of the volume, that is from 1 to 2 liters. But such a degree of abdominal distension alone is of little consequence on the vital capacity as can be seen in Table 6 and in the recent work of Mills (15). However, should the abdominal gas content increase considerably beyond a mere doubling it is likely to limit full inspiration or complete expiration. This may account for the results obtained at 30 and 40 thousand feet equivalent altitude (Table 4) and are comparable to the findings of Eckman and Barach (18) obtained at 35,000 feet. At these altitudes 1 liter of gastro-intestinal gas can theoretically expand to 5 and 7 liters and Mills (15) has indicated that the artificial distension by ingestion of 2 liters of water begins to reduce the vital capacity.

Another factor which may limit the vital capacity is the muscular inefficiency during anoxia (Mosso and Hartmann) which was also demonstrated in respiratory muscles (Table 7). This large functional reduction is probably a central phenomenon, yet the vital capacities measured under identical conditions to those for the muscular efficiency tests showed little reduction in lung volume (Table 3).

The engorgment of pulmonary vessels with anoxia has been cited by many authors to explain the reduced lung volume. Whether such a concept is compatible with the more recent findings of pulmonary vaso constriction and increased pulmonary arterial tensions during anoxia is difficult to evaluate. Verzar (13) has offered a new explanation based upon an increased inspiratory muscle tonus under anoxia which alters the resting position of the lung. This prevents a maximum expiration and thus reduces the vital capacity. This increased muscle tone with anoxia has also been demonstrated on animals (19, 20). It is of interest to note that the average reduction in expiratory reserve volume (2.9%) at 18,000 feet (Table 2) is nearly equal to the reduction of the vital capacity (3.8%) at this altitude and thus gives support to his theory.

If a larger inspiratory muscle tone is responsible for the diminished reduction of vital capacity then it must follow that the residual air volume is increased by an

equal amount. As far as we are aware such studies are not available for acute anoxic exposures. Such measurements might allow one to differentiate between changes in muscle tone and pulmonary engorgment.

Our results with chronic exposure to an altitude of 14,000 feet agree in general with older studies. They differ essentially in 2 points both of which may be ascribed to the volume corrections. Firstly, the maximum change observed is approximately half as small (4%) as those of other authors. Secondly, while many authors indicate only a partial recovery with time we observed a recovery which exceeded the control values. This is of some interest since the studies of Hurtado (21) and Loewy and Wittkower (22) indicate that permanent residents of high altitude have in general a larger vital capacity than sea level dwellers.

Finally, it might be well to point out that the vital capacity changes recorded here and by others approach the range of day to day variability of measurement under so called normal conditions. Thus, Rahn, Fenn and Otis (23) showed that the standard deviation of vital capacity measured daily over a 2-3 months period on 17 individuals ranged from 60-200 ml while Mills (24) shows a similar range when many tests are repeated on the same day.

SUMMARY

A reduction of the vital capacity under acute and chronic exposure to anoxia have been confirmed. However, the absolute volume changes were found to be much smaller than have previously been indicated. This discrepancy may in large part be explained by the failure of previous authors to correct the lung volumes for changes in temperature and water vapor. The maximum changes which were observed in these experiments were approximately 200 ml.

2. Exposure to an equivalent altitude of 18,000 feet reduced the vital capacity by 3.8% while administration of oxygen at this altitude increased the vital capacity. Exposure to 10,000 feet had no significant effect.

3. Similar exposure to the identical inspired oxygen tension breathing oxygen-nitrogen mixtures at ground level showed a barely significant reduction of the vital capacity.

4. Acute exposures to equivalent altitudes of 20, 30 and 40 thousand feet breathing oxygen showed increasingly large reductions of the vital capacity as well as expiratory reserve volumes with and without positive pressure breathing. These reductions are best explained by the increased abdominal distension pushing up the diaphragm and limiting maximum inspiration as well as expiration.

5. Prolonged exposure (7 days) to an altitude of 14,000 feet reduced the vital capacity a maximum of 4% on the 3rd day followed by a recovery beyond the original volume.

6. Artificial distension of the gastro-intestinal tract by 700-800 ml produced no significant change in vital capacity.

7. The maximum force exerted by the expiratory muscles is reduced breathing low oxygen mixtures at ground level.

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CHANGE OF VITAL CAPACITY WITH THE ASSUMPTION OF THE SUPINE POSITION

WILLIAM J. OSHER

THE mechanisms involved in the diminution of the vital capacity and the shift of the respiratory level to a more expired position which accompany the adoption of the supine position have been the subject of some discussion in the literature (1–4). The main possibilities that have been adduced have been reflex and chemical factors, shift in position of the diaphragm, and pooling of blood in the pulmonary bed. There is a decided lack of evidence that reflex and chemical factors are involved and some evidence has been presented that they are negligible (2). The relative importance of the shift of the diaphragm and changes in distribution of blood in accounting for these phenomena, however, still remains a topic for some discussion.

Hurtado and Fray (5) demonstrated on 10 subjects, by means of radiological measurements of the chest, that the resting position of the diaphragm is raised when the supine position is assumed. This is in accord with the spirometric observation that the expiratory reserve[2] is decreased. McMichael and McGibbon (2) made similar measurements to determine the radiological area of the chest in 10 subjects during full inspiration and found no significant difference in the supine position as compared to the erect position. From this observation, and from the fact, which they recorded, that the total capacity of the lungs was diminished in the supine position, they concluded that accumulation of blood in the lungs must account mainly for the diminution of the vital capacity and that a shift in position of the diaphragm accounted for the change in the respiratory level and the inability to expire completely.

The observations of Hamilton and Morgan (1) are somewhat in accord with this view. They showed that the size of the chest in the supine position, measured physically, actually was increased in both deep inspiration and expiration. That blood was a factor in altering the vital capacity was demonstrated by the fact that the standing vital capacity could be increased by the application of blood pressure cuffs, inflated to 70 mm. Hg, to the extremities. This was further developed by Dow (3), who demonstrated in 42 medical students, that about 60 per cent of the loss of vital capacity incident to recumbency could be regained by trapping blood in the extremities with similarly inflated blood pressure cuffs. These last demonstrations are

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[2] Expiratory reserve is used to indicate the amount of air that can be expelled from the lungs following normal expiration by a maximal forced expiration.

inconclusive, however, because in both instances the trunk was made relatively ischemic and the resulting increase in the vital capacity might not necessarily have represented a reversal of the process which originally caused its diminution.

These investigations, particularly those of McMichael and McGibbon, offer evidence which is certainly more than suggestive that pulmonary pooling of blood is an important factor in bringing about the change of vital capacity on recumbency. In the present experiments, some of the characteristics of this decrease in vital capacity were studied and this possibility, as well as the shift in position of the diaphragm, was considered in an attempt to explain the phenomena observed.

METHODS AND PROCEDURES

Eight males and 2 females, young healthy medical students and laboratory workers, were used as subjects. Each of these had had previous experience as subjects for vital capacity measurements. A rebreathing circuit, employing a pen-writing spirometer charged with oxygen, a carbon dioxide absorber and a circulating pump, was used to make records of respirations. During the actual recording of the vital capacity, the carbon dioxide absorber was excluded from the circuit by a valve. Determinations in the erect position were done with the subject relaxed, his back leaning against a tilt table 20° from the vertical plane. Readings in the supine position were taken after tilting the subject passively to a horizontal position. To avoid fatigue of the subject, no readings were taken within one minute of each other except immediately after a change of position. Each experiment was completed within 20 minutes.

The upright vital capacity was determined by the mean of 3 or 4 successive readings. The subject was then tilted to the supine position and serial readings at about one-minute intervals were taken for 10 minutes. The subject was then returned to the erect position and the vital capacity determined as previously.

In a subsequent experiment, 6 healthy subjects, 5 male and 1 female, were tilted by 10° increments from a position 20° from the vertical plane to a horizontal position 90° from the vertical plane and back again through the same intervals. The subjects were allowed to remain in each position for less than 1 minute and the vital capacity was recorded.

The values obtained from the spirometric readings were corrected to body temperature, pressure and vapor pressure.

RESULTS AND DISCUSSION

The mean values for the 10 subjects indicated that 184 cc., or about 54 per cent, of the vital capacity loss of 341 cc. incident to the adoption of the supine position was regained, when this position was maintained for 10 minutes. This gain was statistically significant in 7 of the 10 subjects, if one uses the standard deviation of the determination of their erect vital capacity as a measure of the accuracy of the figures for the gain. A similar significant increase of the vital capacity over its original erect value was seen when the erect position was resumed. This amounted to 132 ± 24.2 cc.

A marked diminution, 860 cc., of the expiratory reserve was noted with recum-

bency which underwent no significant change while the supine position was maintained. On resumption of the upright position, however, the expiratory reserve fell short of attaining its original erect value by 171 ± 60.1 cc.

The observation of the vital capacity and the expiratory reserve was continued for about 3 minutes after the erect position was resumed. No great change was noted

TABLE 1. MEAN VALUES OF THE VITAL CAPACITY FOR THE ERECT POSITION, FOLLOWING RECUMBENCY AND ON RESUMPTION OF ERECT POSITION

SUBJECT	ERECT	SUPINE (MIN.)					ERECT
		0-1	2-4	4-6	6-8	8-10	
L. M. C.	5310 ± 66	4900	5100	5050	5150	5200	5410 ± 170
W. E. S.	4810 ± 10	4300	4250	4550	4470	4885	4790 ± 195
D. H.	4855 ± 92	4800	4850	4840	4830	4760	4895 ± 34
D. L.	4840 ± 70	4420	4550	4455	4610	4635	4960 ± 53
G. K.	4340 ± 88	4095	4030	4200	4245	4360	4415 ± 75
L. B. E.	4400 ± 103	4300	4560	4565	4715	4855	4935 ± 82
B. D.	5010 ± 88	4740	4150	4250	4920	4545	5290 ± 28
J. A. R.	5770 ± 14	5405	5450	5400	5550	5450	5870 ± 57
R. C.	5340 ± 78	4805	4900	4975	5005	5000	5360 ± 28
S. B. G.	6140 ± 58	5730	5810	5900	5780	5760	6205 ± 72
Mean	5091 ± 23	4750	4749	4818	4927	4934	5214 ± 26

TABLE 2. MEAN VALUES OF THE EXPIRATORY RESERVE FOR THE ERECT POSITION, FOLLOWING RECUMBENCY AND ON RESUMPTION OF ERECT POSITION

SUBJECT	ERECT	SUPINE (MIN.)					ERECT
		0-2	2-4	4-6	6-8	8-10	
L. M. C.	2300 ± 145	1245	1040	1080	1100	995	2060 ± 110
W. E. S.	1850 ± 73	890	1006	1420	980	1350	1660 ± 85
D. H.	1760 ± 80	1370	1180	1210	1255	1120	1620 ± 87
D. L.	2190 ± 74	965	900	830	770	830	2770 ± 186
G. K.	1585 ± 108	800	750	815	720	950	1420 ± 60
L. B. E.	1650 ± 44	1240	1335	1310	1200	1360	1610 ± 202
B. D.	2065 ± 84	1460	1270	1255	1165	1255	1680 ± 51
J. A. R.	2690 ± 200	1030	1030	1025	1100	1100	2420 ± 54
R. C.	1430 ± 51	750	835	910	960	955	1410 ± 101
S. B. G.	1825 ± 37	995	860	760	775	720	1640 ± 111
Mean	1934 ± 57	1074	1020	1075	1005	1065	1729 ± 63

in these measurements with time and it was assumed that they exhibited no directional trend during this period. This was borne out by the standard deviation of their values, (±25.8 cc. for the vital capacity and ±60.1 cc. for the expiratory reserve), which were within the usual range for spirometric observations.

These observations suggest that definite and persisting changes affecting the space available for air in the chest took place while the relaxed supine position was

maintained. It is possible that this might represent a shift of blood away from the lungs. Against this, however, there is the observation that the cardiac output increase of 25 to 30 per cent, which is generally believed to occur in the supine position, is maintained for at least 15 minutes (6). McMichael and McGibbon (2) stated that a high pressure in the pulmonary veins must be maintained in order to insure an adequate venous return to the left side of the heart under these conditions. It would seem that persistence of the pulmonary pool would be a likely means of accomplishing this. Cotton (7, 8) has also observed a cephalad movement of the center of gravity, more marked after exercise, in his subjects following recumbency. This, he presumed to be due mainly to the movement of blood and lymph away from the legs.

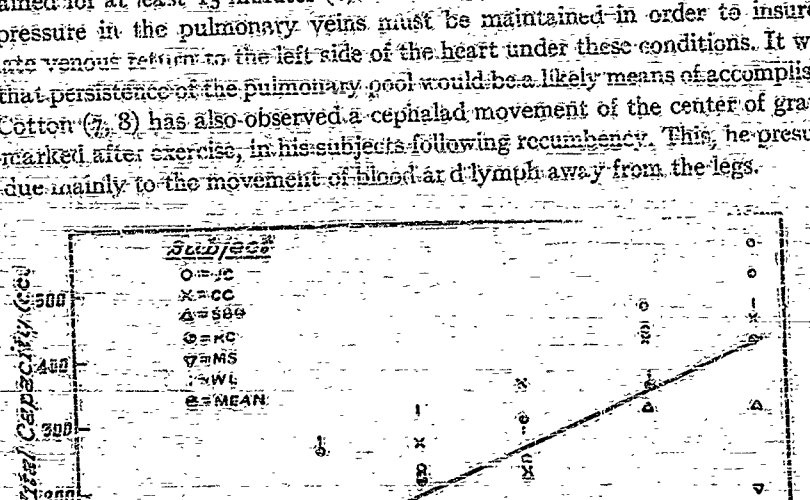

Fig. 1. Relationship between the diminution of the vital capacity and the vertical distance between the subjects' feet and pulmonary bed expressed as 1 — cos. angle.

Neither of these possibilities, however, represents an insuperable obstacle to the movement of blood away from the lungs by active constriction of the pulmonary vessels, the blood flow being maintained by a rise in pressure.

The likelihood that this represents an alteration of the mechanics of respiration does not seem great. Hamilton and Morgan (1) showed, by placing their subjects on a scaffold on which only the vertebral column and the shoulders were supported, that there was no demonstrable decrease in the vital capacity resulting from pressure of the chest against a table in recumbency. The persistence of an unchanged expiratory reserve in the supine position makes the possibility that the diaphragm has assumed a new and more effective position seem unlikely. This would require a new length-tension relationship and would be reflected in a change in the respiratory level.

The probable role of pulmonary pooling of blood, in the reduction of the vital capacity, suggests that the hydrostatic effects incident to recumbency might be an

important factor. If this were so, the diminution of the vital capacity could be correlated with the vertical distance between the feet and the pulmonary vascular bed. This hypothesis was tested by putting 6 subjects through a series of tilts as described.

In analyzing the results of this experiment, it was noted that the vertical component between the feet and the pulmonary vessels could conveniently be expressed as the cosine of the angle designating the subject's position. Since the hydrostatic effects tending to diminish the vital capacity would theoretically be least when the cosine of the angle is 1, that is, when the subject is erect and the angle to the vertical plane is 0°, any change tending to produce a hydrostatic effect different from the erect position could be expressed as 1 − cos. angle. Accordingly, a correlation was sought between 1 − cos. angle and the diminution of the vital capacity.

The mean values for the vital capacity of the 6 subjects were determined for each position and the mean diminution of the vital capacity was calculated for each of these positions. These were plotted against the trigonometric function as expressed above. A line was fitted to these points for each position by the method of least squares. The standard error in estimating the value of the trigonometric function was 0.038 and the significant correlation coefficient of 0.902 was obtained.

These results would suggest that the factor responsible for the loss of vital capacity in the supine position is one which can be expressed and quantitated in hydrostatic terms. Whether it acts on the venous return, on the diaphragm in the form of pressure of the abdominal viscera, or some unknown mechanism or on any combination of these, of course, has not been demonstrated by this experiment. That the diaphragm is subjected to pressure of the viscera seems to be rather well indicated by the fact that its position has shifted and this must imply a new length-tension relationship. That there is an effect on the venous circulation seems to be indicated by the increase of the cardiac output in the supine position. If one considers McMichael and McGibbon's demonstration that there is important pulmonary pooling, it would further suggest that the pressure-volume relation of the pulmonary vessels, within this physiological range, is such that a linear response is obtained to the increased hydrostatic forces of the supine position on the vessels.

These are possibilities that require further investigation.

SUMMARY

Successive measurements of the vital capacity of 10 subjects in the supine position revealed that about 54 per cent of the mean loss of 341 cc. incident to the adoption of this position was regained in 10 minutes. The expiratory reserve likewise decreased a mean amount of 860 cc. and remained unchanged while the supine position was maintained. An increase in the vital capacity and a decrease of the expiratory reserve as compared to their previous erect values were found when the upright position was resumed.

A high correlation between the vertical component of the arc through which the body moves in assuming the supine position and the diminution of the vital capacity was demonstrated in 6 subjects.

Some of the mechanisms that might be involved were discussed.

The author wishes to express his gratitude to Dr. W. O. Fenn, who has contributed much to the preparation of this work.

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THE EFFECT OF A BRIEF PERIOD OF VOLUNTARILY INCREASED PULMONARY PRESSURE UPON VITAL CAPACITY

by

Henry T. Bahnson*

Numerous procedures have been shown to alter temporarily the vital capacity, e.g. posture (1-5), tourniquets (2-4) or bandages (6) upon the extremities, venesection (7,8), immersion in water (9), drugs such as adrenalin (10), amyl nitrite and vasopressin (11,12), changes of environmental temperature (13), and positive and negative pressure breathing (12). It has been generally considered that the vital capacity reflects inversely changes in the amount of blood in the lungs. The present work deals with alterations in vital capacity caused by a brief period of voluntarily increased pulmonary pressure in the erect and supine positions.

METHOD

Eight normal males aged 21 to 37 served as subjects. Maximal expiration from full inspiration was measured in a collecting spirometer. The effect of increased pulmonary pressure was studied by having the subject inspire maximally; then with care to keep the glottis open he blew against a mercury manometer, rapidly raising the pressure to 40 mm. Hg and maintaining it for 5 seconds. Immediately after this procedure an additional volume of air could be inspired and expiration quickly performed into the spirometer. Change of position was effected on a tilt table. All measurements were made in the resting state.

Two to 4 measurements of vital capacity were made in order at 1 minute intervals under each of the following conditions: (1) Erect, control, (2) Erect following increased pulmonary pressure, (3) Erect, control, (4) Supine, control, (5) Supine after increased pulmonary pressure, (6) Supine, control, (7) Erect, control. This plan of determinations was repeated on 4 or 5 days. All values were corrected to BTPS.

The mean value for the three erect control determinations was compared with the value after increased pulmonary pressure while erect and with the supine control. The latter measurement was compared in turn with the value after increased pressure while supine. The probability of significant difference between these values was estimated by the Fisher T-test (14). The smallest number of determinations subjected to statistical analysis was 8, the largest 30.

RESULTS

Results are summarized in the table. A graphic record is shown in Figure 1. In all but one subject (J.L.) raising pulmonary pressure to 40 mm. Hg for 5 seconds immediately prior to expiration caused a significant increase in vital capacity in the erect position; the average increase was 147 cc. or 2.71 percent with one S.D. of

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Effect of Increased Pulmonary Pressure on Erect and Supine Vital Capacity

Subject	Erect: Control V.C. in liters ±S.D.	Erect: After increased pulmonary pressure[1]	Erect: Significance of increment[2]	Supine: Control[1]	Supine: Significance of decrement[2]	Supine: After increased pulmonary pressure[1]	Supine: Significance of increment[3]
A.O.	5.17 ± .09	+1.93	$P < .01$	- .04	$.5 < P < .6$	+2.11	$P < .01$
A.S.	5.13 ± .12	+4.10	$P < .01$	-5.98	$P < .01$	+7.33	$P < .01$
C.M.	4.87 ± .14	+3.49	$P < .01$	-6.55	$P < .01$	+6.96	$P < .01$
H.B.	5.95 ± .09	+1.68	$.01 < P < .12$	-6.55	$P < .01$	+4.76	$P < .01$
H.R.	6.19 ± .13	+1.94	$.01 < P < .02$	-3.87	$P < .01$	+5.48	$P < .01$
J.D.	5.17 ± .18	+4.45	$P < .01$	-3.36	$.2 < P < .3$	+10.16	$P < .01$
J.L.	5.84 ± .17	+1.03	$.3 < P < .4$	-7.34	$P < .01$	+5.30	$P < .01$
W.D.	5.23 ± .11	+3.06	$P < .01$	-4.75	$P < .01$	+2.85	$P < .01$
Average ±S.D.	5.44 ± .14	+2.71 ± 1.15 or 147 cc.		-4.80 ± 2.38 or 261 cc.		+5.62 ± 3.64 or 306 cc.	

1. Mean increments and decrements expressed as percent of erect control.
2. Compared with erect control by Fisher T-test(14).
3. Compared with supine control by Fisher T-test.

Figure 1

Spirographic tracing to show effect of voluntarily increased pulmonary pressure upon vital capacity. The 408 ml between A and B represents the additional volume inspired after 5 seconds of increased pressure.

1.15 percent of the erect control vital capacity. When tilted to the horizontal position 7 of the 8 subjects showed a decrease in vital capacity, one of which was statistically insignificant, and one showed no change; the average decrease was 261 cc. or 4.80 ± 2.38 percent of the erect control value. Increased pulmonary pressure while recumbent caused a significant increase in vital capacity in all instances, the average being 306 cc. or 5.62 ± 2.64 percent of the erect control.

Preliminary experiments on one subject showed no change in vital capacity after maintaining the position of maximal inspiration for 5 seconds with the glottis open and without increased pulmonary pressure. A pressure of 40 mm. Hg was selected simply as a matter of convenience and comfort; there seemed to be no significant difference in preliminary experiments if this value was altered between 90 mm. Hg and a relaxation pressure around 20 mm. Hg. Similarly 5 seconds was selected, no difference being noted between 5 and 15 seconds. On several subjects no consistent effect on vital capacity could be demonstrated by maintaining a near maximal negative pressure throughout inspiration.

DISCUSSION

Various means have been described of altering the vital capacity and correlating such changes with shifts of blood from or to other regions of the body. Hamilton and Morgan showed an approximately 300 cc. difference between the average erect and supine vital capacity. This difference could be made to diminish or disappear if tourniquets were applied to the extremeties and blood trapped there. These findings have been confirmed and amplified by workers cited earlier. Budelman (7) showed that a venesection increased the vital capacity and commented on the clinical use of tourniquets as a "bloodless venesection." In a large number of blood doners Glaser and McMichael showed that a 380 cc. loss of blood was accompanied by an average increase of 153 cc. in vital capacity and 181 cc. in total pulmonary capacity. Sjöstrand (11) studied the effects of various drugs and showed that in the reclining position the vital capacity was increased by a fall in blood pressure as caused by amyl nitrite, or an increased cardiac output as caused by adrenalin or ephedrine. He believed the lungs had a sort of "Blutdepotfunktion" and suggested they were the only organs which could absorb blood from the legs when position was changed from erect to horizontal. Mills found that one minute of negative pressure breathing caused a decrease of 100 to 300 cc. in vital capacity. He could demonstrate no significant change with periods of positive pressure breathing or a single inspiration under positive or negative pressure.

From the data presented here it is apparent that the vital capacity increases significantly after 5 seconds of voluntarily increased pulmonary pressure. One

cannot state whether this change is due to obstruction of venous return, expression of blood from the lungs, or a combination of both factors. If obstruction of venous return were the main factor, the right ventricular output would have to be essentially nil during the 5 second period, assuming a cardiac output of 80 cc. per second. If this were true, there should be no significant difference between the erect and supine increments. It seems more likely that a fraction of the total pulmonary blood volume can be expressed from the depot. The gain in vital capacity after a period of voluntarily increased pulmonary pressure while supine is approximately twice that while erect and is greater than the loss in vital capacity on assuming the horizontal. This suggests a larger depot while recumbent than when erect.

SUMMARY

An increase in pulmonary pressure to 40 mm. Hg maintained for 5 seconds in the inspiratory position immediately prior to measurement of vital capacity causes an average increase of 147 cc. or 2.71 percent with one S.D. of 1.15 percent of the normal control vital capacity while erect. When recumbent this value is 306 cc. or 5.62 ± 2.64 percent of the erect control. An average reduction of 281 cc. or 4.80 ± 2.38 percent of the vital capacity occurs on assuming the recumbent position from the erect.

The significance of these findings is discussed in connection with the volume of blood in the lungs in the erect and recumbent positions.

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LUNG VOLUME CHANGES WITH POSITIVE AND NEGATIVE PULMONARY PRESSURES

by

R. C. Fowler, M. Guillet, H. Rahn

Evidence has been presented by Fenn et al (1) in tester board studies of a displacement of about 500 cc. of blood from the lungs to the abdomen and extremities during positive pressure breathing (30 cm. H_2O). More recently Fenn (2) has suggested that such blood shifts could be incorporated in pressure-volume diagram of the lung (3). That such shifts in the pulmonary pool may be demonstrated by changes of similar magnitude in the vital capacity was suggested by Bahnson (4) who showed that an increase in pulmonary pressure to 40 mm. Hg (Valsalva maneuver) maintained for 5 seconds in the full inspiratory position immediately prior to the measurement of vital capacity causes an increase of about 2.71% in the erect and 5.6% in the supine position.

The present study deals with careful measurements of lung volume changes as a function of sustained positive and negative pressure breathing as well as following the Müller and Valsalva maneuvers of varying effort and their interpretation in terms of shifts in the pulmonary blood pool.

METHODS AND DEFINITIONS

Three methods were used in an attempt to prove and measure the existence of blood shifts to or from the lungs with pressure breathing.

1a. The Müller maneuver produces an acute negative pulmonary pressure under voluntary control and is herein defined as a forced inspiration against a recording mercury manometer following a maximal forced expiration. After maintaining a constant negative pressure for 5 seconds one is capable of expiring an additional volume into a small recording spirometer. The sequence of these events is controlled by a four-way stopcock. This maneuver as well as the Valsalva was carried out in the sitting position.

1b. The Valsalva maneuver produces an acute positive pulmonary pressure under voluntary control and is herein defined as a forced expiration against the recording mercury manometer following a maximal inspiration. After maintaining a constant pressure for 5 seconds one is then capable of inspiring an additional volume from the spirometer.

2. Continuous positive (PPB) and negative (NPB) pressure breathing was achieved with an early model of the Drinker respirator. The subject was connected with a closed breathing circuit having a circulating pump, CO_2 absorber and a 12 liter recording spirometer filled with oxygen.

3. Residual air volume measurements were carried out while under PPB and NPB by the nitrogen dilution method of Rahn et al (5).

All volumes were corrected to BTPS (Body Temperature Pressure Saturated) and the vital capacity recorded as percent of that determined under normal conditions for each individual.

OBSERVATIONS

1. While the Müller maneuver was followed invariably by a further displacement of air into the spirometer, the Valsalva maneuver was followed by a further intake of air from the spirometer. These volume decrements and increments are highly significant (Table 1) and seem to vary with the applied pressures over the range of +20 to +[illegible] cm H_2O (Fig. 1).

TABLE 1

The Additional Volume Inhaled After a Valsalva Maneuver (+) and the Additional Volume Exhaled After a Müller Maneuver (-) When the Pressures Were Varied From +40 to -50 mm Hg. The Lung Volume Changes are Expressed as % of Normal Vital Capacity. The P Values of These Volume Changes is Less Than 1% in Each Pressure Range. Subjects in Sitting Position.

Pressure mm Hg	% Change in V.C.	Standard Deviation	Standard Error	Number of Observations
+40 to +30	+2.46	±0.53	0.24	5
+30 to +20	+1.90	±0.99	0.31	10
+20 to +10	+2.18	±0.91	0.24	15
+10 to +0	+0.99	±0.86	0.28	10
0 to -10	-0.82	±0.47	0.13	13
[illegible]	[illegible]	±0.98	0	16
[illegible]	[illegible]	±0.45	0	[illegible]
[illegible]	[illegible]	±0.49	0.15	11
-50	-2.08	±0.52	0.23	5

[illegible] with continuous pressure breathing [illegible] subjects were able to expire maximal[illegible] and to the same apparent lung volum[illegible] regardless of the pressure applied (F[illegible] Fig. 2) On the other hand, the maxi[illegible] inspiratory position became progressively limited with increasing negative pu[illegible]ary pressure but larger with increasing positive pressure (Fig. 2 and Table 2

[illegible]ring a continued maximal expirato[illegible]ffort, there was no further change in [illegible]spirometer volume when the press[illegible]re suddenly released. However, [illegible]g a maximal, continued inspiratory eff[illegible] apparent lung volume increased [illegible] release of negative pulmonary pressure [illegible]creased with release of positive [illegible]monary pressure (Fig. 2).

3. Residual air volume measurements d[illegible]ntinuous pressure breathing [illegible]wed a slight decrease during NPB. During [illegible]n increase of considerable [illegible]gnitude was observed with little additional [illegible]eyond 20-30 mm. Hg. (Table 2).

TABLE 2

Changes in Vital Capacity and Residual Air Volume With Continuous Pressure Breathing (Subject Supine in Respirator)

Subject	% Vital Capacity					Residual Air as % V. C.			
Pressure (cm H_2O)	ABD	RCF	MS	TM	Mean	ABD	RCF	TM	Mean
+45						37.2	36.5	42.5	35.7
+40	103.0	105.9			104.5				
+30	104.0	102.8	106.6	103.5	106.0	29.5	36.0	43.0	36.2
+20	103.5	107.5	104.5	105.7	105.3				
+15						27.1	32.8	35.0	36.1
+10	100.5	105.5	104.3		103.5				
atmos.	100.0	100.0	100.0	100.0	100.0	26.4	27.2	33.0	26.7
-10		101.5	97.0	99.4	99.3				
-15						25.6	26.6	32.5	26.3
-20	89.0	93.4	89.2	92.6	91.1				
-30	92.0	85.7	82.2	92.6	88.1	24.8	26.7	30.1	27.2
-40	88.9	71.5			80.2				
-45						35.5	27.1	29.2	27.3
-50		61.3			61.3				

DISCUSSION

The results obtained are most easily discussed with reference to Fig. 3. This pressure-volume diagram has been revised to conform with the results obtained in this study. The changes in blood volume have been obtained "by subtraction." Consequently it is important to establish some anchor points first which may permit such a procedure. The lung tissues may be regarded as incompressable and will therefore occupy a rectangle of a certain thickness and serve as a base of our construction. The absolute volume is not important and has been estimated at 1200 cc. The pulmonary blood pool follows as the next category and has been assumed to occupy at zero (atmospheric pressure) 1000 cc. Again, for our purposes, the absolute volume is not important since our interest is centered upon changes of this quantity. The next category is the residual air volume followed by the subdivisions of the vital capacity. The fact that the continuous spirometer records (Fig. 2) indicate that with both positive and negative pressure breathing the maximal expiration (zero vital capacity) returns the chest to the identical volume furnishes us with an additional base line. This one may assume to run parallel to the lung tissue line. Thus, the residual air volumes may be plotted from the zero vital capacity line. The only

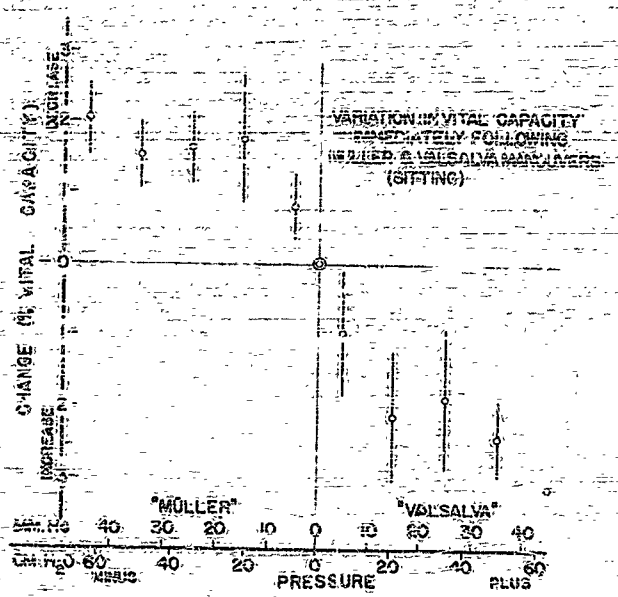

Figure 1

Additional air expelled and inhaled immediately following a Müller and Valsalva maneuver respectively. The various pressures applied are plotted on the abscissa. The volumes are expressed as % changes of vital capacity and designated as a decrease (Müller) or increase (Valsalva) of the vital capacity.

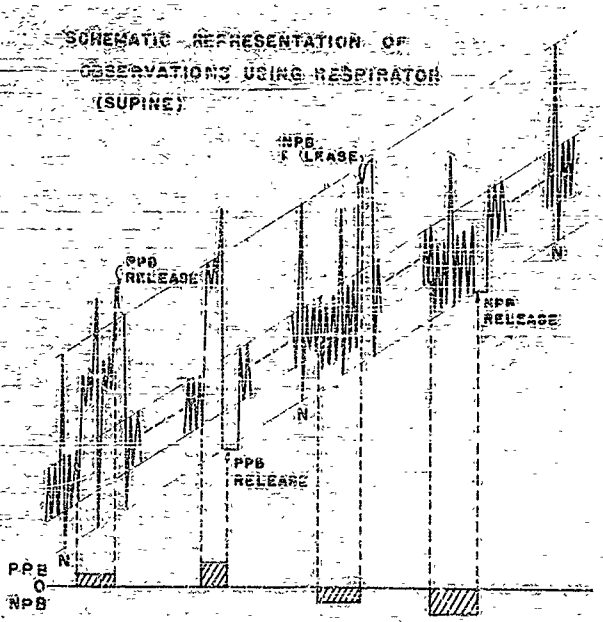

Figure 2

A schematic representation of lung volumes recorded on a rebreathing circuit during continuous positive and negative pressure breathing. Inspiration is upward. The slope of the base line represents the oxygen-consumption.

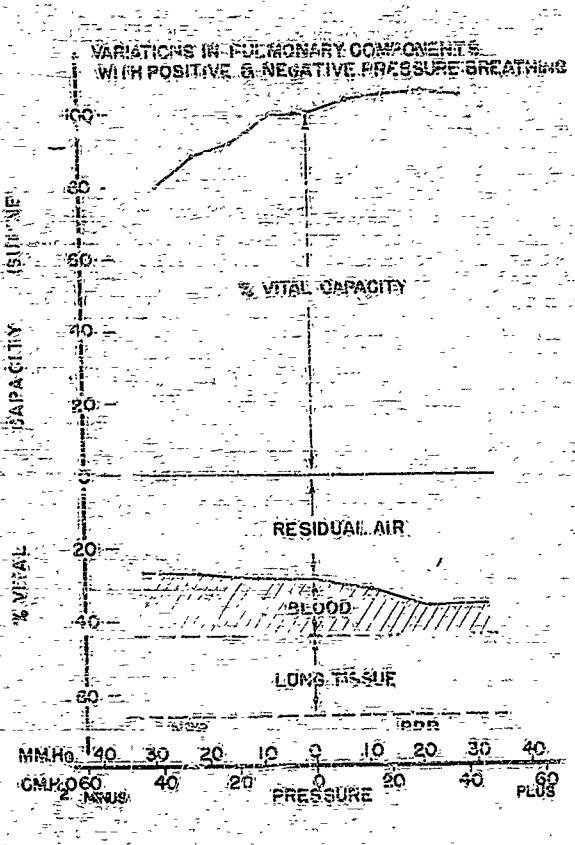

Figure 3.

The Pressure-volume diagram of the lung (supine). All values are recorded as % normal vital capacity during continuous positive and negative pressure breathing. For discussion see text.

remaining space between the residual air volume and the lung tissue volume is presumably the lung blood volume (shaded area = Fig. 3).

The changes in the pulmonary blood pool arrived at by this method mirror very closely the volume-pressure curve of the Müller - Valsalva experiments (Fig. 1). We have assumed, as Bahnson (4) has suggested, that the latter are also the results of pulmonary blood shifts. The maximal blood displacement with continuous positive pressure breathing is 7% of the vital capacity volume when estimated by the residual volume changes. This is approximately 340 cc in absolute volume and agrees well with Fenn's evaluation of 500 cc (1). For the Valsalva maneuver in the supine position we have only the figures of Bahnson (4) which show an average displacement of 5.6% or 300 cc. With the subject in the supine position the agreement of these methods, the teeter board (1), the Valsalva maneuver (4) and our residual air volume measurements is fairly good particularly in view of the rather indirect and crude methods of each procedure.

In the sitting position one may expect approximately half the blood shift with positive pressure breathing. Our maximal displacement of 2.5% of the vital capacity agrees well with the figure of 2.7% obtained by Bahnson.

The vital capacities during pressure breathing were recorded either by the usual procedure of exhaling the maximal volume after a full inspiration or by recording on the drum the sudden volume changes which resulted upon release of pressure while the maximal inspiratory effort was still maintained (see Fig. 2). The latter method was less fatiguing and yielded the same results when the volume changes caused by the release of pressure were added or subtracted from the normal vital capacity. The results are given in Table 2. The vital capacities were plotted by adding the volumes to the zero vital capacity line in Fig. 3. With negative pulmonary pressures the vital capacity is markedly reduced as has been pointed out previously (3) and with positive pulmonary pressure this volume is slightly increased. The increase with positive pressure was not observed previously (3) but was recently demonstrated by Mills (6).

The fact that the continuous spirometer recordings (Fig. 2) indicate the ability to expire maximally to the same apparent volume under positive as well as negative pressure requires some further discussion. It had been previously predicted (6) that one would be unable to expire completely under positive pressure due to the limitation of the expiratory muscles at these very small lung volumes. These experiments, however, suggest that this is not true over the range from -0 to +30 mm Hg. On the other hand, one of us breathed up to +40 mm Hg and in this range it could be seen that the normal maximal expiratory position could no longer be attained. From this pressure on upward the residual air volume would increase further not due to pulmonary blood shifts alone, but at the expense of the expiratory reserve volume as has been previously suggested (3). Furthermore, the ability to expire maximally to the same apparent lung volume with and without pressure seems incompatable with simultaneous changes in the residual air volume. If a subject, breathing normally in a closed rebreathing circuit, is shifted to positive pressure breathing any increase in the residual air volume must be absorbed by the gas volume of the closed circuit. This fact by itself should alter the base line to which a subject could maximally expire. Yet this was not observed (Fig. 2).

SUMMARY

1. Changes in the vital capacity were measured after a voluntary application of positive (Valsalva) and negative (Müller) intra pulmonary pressures. These changes suggest that a certain volume of blood can be expelled or aspirated respectively into the chest cavity. The volume changes are a function of the pressure applied over the range of -20 to +20 mm Hg. Application of greater pressure seems to have no further effects upon volume changes.

2. With continuous positive and negative pressure breathing the residual air volumes as well as the vital capacities become larger and smaller respectively. An interpretation of these findings in terms of shifts of the pulmonary-cardiac blood pool is given together with a pressure volume diagram of the lung which includes the tissues, blood and gas volumes.

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THE BURNING OF CO TO CO_2 BY ISOLATED TISSUES AS SHOWN BY THE USE OF RADIOACTIVE CARBON

ROBERT T. CLARK, JR., J. NEWELL STANNARD AND WALLACE O. FENN

IN 1931 Fenn and Cobb (1) presented evidence that the stimulatory action of carbon monoxide on the respiration of frog and rat skeletal and cardiac muscle (2) was due to oxidation of carbon monoxide to carbon dioxide. Their conclusions were based upon a comparison of the total gas disappearing from a closed respirometer system, as measured by the associated volume decrease, with the oxygen disappearing as measured by direct gas analysis.

The stimulatory action of CO on muscle respiration and factors influencing the process were studied in some detail by subsequent authors (3–5). No experimental evidence has appeared which negates the conclusion that muscle tissue can accomplish the oxidation of CO to CO_2. However, the original evidence was sufficiently indirect to make direct confirmation desirable. With the availability of the long-lived C^{14} isotope and adequate methods for its measurement a direct approach was possible and the results of such studies are described in part in this paper. They constitute both qualitative and quantitative confirmation of the presence and magnitude of this phenomenon in various tissues deduced by earlier indirect methods.

METHODS

In general the technique consisted in measuring *in the same* experiment: 1) the total gas consumed by the tissues in the presence of a CO-O_2 mixture, subtracting from this the amount of oxygen consumed in air over an equivalent period and 2) the radioactivity of the CO_2 collected during exposure to the CO-O_2 mixture (which contained $C^{14}O$), and calculating the amount of CO which would have been oxidized to produce the measured amount of activity in the CO_2 collected. The gas consumption measurements were made in the special differential volumeter described by Fenn and Cobb (1) with slight modifications described by Stannard (5) and Clark (6). Essentially this is an ordinary volumeter arranged to permit resetting of the index drop without opening the apparatus to air, thus permitting larger changes in volume and composition of the contained gases than is possible with only one traverse of the capillary tube.

The CO_2 produced during the period in CO was collected in a small vial of barium hydroxide placed in the center well of the respirometer. This was removed with minimal exposure to laboratory air and placed in a sealed container for transport to the C^{14} measuring apparatus. The latter consisted of an ionization chamber about 1500-

ml. capacity in which the activity of the released CO_2 gas was measured after passage through a suitable purification train. Details of this apparatus are being described by Bale *et al.* (*7*).[2]

The radioactive CO was prepared from barium carbonate[3] (specific activity about 3 μc/gram carbon) by adding concentrated sulfuric acid in a suitable generator which was connected in turn to a tube containing zinc and asbestos kept at 475°C. in a muffle furnace for reduction of the released CO_2 to CO after the method of Bernstein and Taylor (*8*). The entire system was evacuated before use (Cenco Hy-Vac pump) and the gases were transferred through the system by manipulation of mercury-filled tonometers. In practice it was found that five passages of the released CO_2 through the reducing tube accomplished complete conversion to CO. Final storage of the CO was made in tonometers containing 50 cc. of 1 M NaOH over the mercury to insure removal of any remaining traces of CO_2.

The gas mixture contained 80 per cent CO and 20 per cent O_2, a composition giving maximal stimulation of muscle respiration in earlier work. The following procedure was used to avoid loss of radioactive CO into the laboratory and to conserve material: pure oxygen was passed through the experimental bottle of the respirometer until all the other gases were flushed out. $Ba(OH)_2$ was then added to the vial within the central well of the bottle. This procedure prevented the $Ba(OH)_2$ from being exposed at any time to the CO_2 of the atmosphere. The tonometer containing the CO was then connected to the bottle and the oxygen permitted to flow from the respirometer through the connection to the tonometer and on through the stopcock to the atmosphere. All stopcocks were then closed and the experimental bottle plus connections to the tonometer were evacuated to 20 per cent of an atmosphere. The CO was then allowed to enter the respirometer until the pressure was again atmospheric.

Rates of CO burning were calculated from the C^{14} measurements as follows:

$$\text{ml. CO in experimental sample} = \frac{\mu\text{c. in experimental sample}}{\mu\text{c/ml. CO in original mixture}}$$

where:

$$\mu\text{c/ml. CO in original mixture} = \frac{\mu\text{ c/gram } BaCO_3}{\text{ml. CO obtained from one gram } BaCO_3}$$

and:

μc in experimental sample is measured directly.

then:

$$\text{mm}^3 \text{ CO burned/gram tissue/min.} = \frac{\text{ml. } CO_2 \text{ in exper. sample} \times 1000}{\text{wet wt. tissue in gm.} \times \text{time in min.}}$$

[2] Particular thanks are extended to Dr. W. F. Bale and his assistants Miss June Levin, Mrs. H. C. Stebbins and Mr. L. R. DeLaVergne for performing the C^{14} measurements.

[3] Supplied by Dr. R. W. Heimkamp, University of Rochester, Department of Chemistry.

Owing to the small amounts of CO_2 collected it was necessary to add carrier CO_2 in the C^{14} apparatus and no attempt was made to measure volumes of CO_2 collected. Thus no measure of R. Q. was possible in these experiments.

In practice two types of experiment were performed: 1) Where matched tissues (e.g. paired muscles) were obtained two respirometers were used, one for the CO-O_2 mixture and the other for measurements in air. There was thus a continuous control for observing the rates in air, and this rate was subtracted from the rate in CO for computation of the 'excess' metabolism in CO.

2) Where matched tissues were not obtained only a single volumeter was used and the rate of oxygen consumption was measured first for two hours in air, then a fresh barium hydroxide vial was inserted, the CO-O_2 mixture placed in the gas space as described above, and the gas consumption was followed for periods determined by the rates observed. Then the $Ba(OH)_2$ vial was removed and replaced and the gas consumption followed for another hour in air. The average rate in air before and after the period in CO was subtracted from the rate in CO mixture to obtain the 'excess' in CO.

No distinction is made between these methods in reporting the results since no essential differences were found. While rates of gas exchange were not always constant with time the comparison of respirometer and isotope data does not require that this be rigidly true. However, to insure as nearly constant rates as possible all tissues (frog) were dissected the evening before the experiment and kept in Ringer-phosphate at 5°C. overnight, following the technique of Stannard (9). The vessels contained 3 ml. of Ringer-phosphate at *p*H 7.3. The solutions, including inhibitors, were prepared as described by Stannard (9).

Further details regarding certain control experiments are described with the results.

RESULTS

Comparison of CO Oxidation Rates Measured by Respirometer and Isotope Methods. Table 1 presents the essential results obtained with frog skin, nerve and skeletal and cardiac muscle. The fifth and sixth columns give the rates of gas consumption of the tissues measured in the respirometer in air and in the CO-O_2 mixture. The difference between the two (column 7) represents the excess gas consumption due to the presence of the CO-O_2 mixture. The figures in this column indicate a very slight increase in gas consumption with nerve but a large increase with heart and skeletal muscle. Skin remained unchanged after the addition of the CO-O_2 mixture. Column 8 gives the total radioactivity obtained from the collected CO_2 after correction for the small amounts of activity found in the alkali in control experiments without tissue (*Exper. 4* and *16*). These data are expressed as disintegrations per minute and represent the radioactivity of all of the CO_2 collected during the period in CO-O_2 mixture. Because of the need for adding inert carrier CO_2 (see above), these figures are not referred to specific volumes of gas; but this does not affect their usefulness. In the last column the amount of CO burned to CO_2 has been calculated from the activity measurements of the various tissues and the rate of burning expressed in cu. mm/g/minute. The

rate of burning was highest in heart and skeletal muscle, considerably lower in nerve, and negligible in skin.

A comparison of the CO burned as determined by the radioactive isotope with the excess gas consumption obtained with the respirometer shows that the isotope measurements in every case give smaller values. However, the values for the isotope only represent the amount of CO burned by the tissues and in order to be comparable to the excess gas consumption 1/2 mol of oxygen would need to be added to each mol of CO burned. This comparison is made in figure 1, in which the excess respiration as calculated from the isotope measurements is plotted against the excess determined from the respirometer. The points all fall along a straight line through the origin with

TABLE 1. BURNING OF CO TO CO_2 BY RBCC TISSUE IN 80 PER CENT CO AND 20 PER CENT O_2, VOLUMETRIC METHOD (RESPIROMETER) COMPARED WITH ISOTOPE (C^{14}) (RINGER-PHOSPHATE AT *p*H 7.3, 28°C.)

EXPER.	TISSUE	WEIGHT	TIME	RESPIROMETER			ISOTOPE (C^{14})	
				Air[1]	CO[1]	Δ[2]	CO^2	CO burned
		gm.	*min.*				*c/min.*	
11	Skel. muscle	.68	300	0.18	0.31	0.13	1160	0.10
10	Skel. muscle	.69	300	0.23	0.44	0.21	1429	0.11
132	Skel. muscle	.53	300	0.26	0.53	0.27	1673	0.17
5	Skel. muscle	.87	540	0.27	0.65	0.38	10525	0.30
14	Heart	.13	300	0.87	1.76	0.89	1297	0.56
12	Heart	.20	300	0.49	1.71	1.22	2764	0.76
9	Heart	.23	300	0.76	1.92	1.16	2651	0.63
8	Heart	.40	480	0.41	1.30	0.89	7629	0.65
7	Nerve	.31	600	0.26	0.23	0.02	251	0.03
6	Skin	.80	540	0.30	0.39	−0.01	105	0.003
4	Control						75.1	
16	Control						169.0	

[1] mm^3/g/min. [2] After correction for Control. Radioactive disintegrations per minute.

a slope of 1.0, thus indicating that the increase in gas consumption brought about by the addition of the CO-O_2 mixture to the respirometer is due primarily to the burning of CO to CO_2.

It will be noted that the maximal rate of CO oxidation occurs with cardiac muscle, intermediate rates with skeletal muscle, and that there was only slight evidence of oxidation with nerve and practically none with skin. In fact the rates with skin and nerve may be considered within the limits of experimental error of the respirometer. The counts yielded in the isotope measurements with these tissues approximated twice the background and control corrections thus indicating the possibility of small amounts of CO oxidation, but essentially the phenomenon may be considered as characteristic of skeletal and cardiac muscle. This confirms previous work and, since the correlation between respirometer and isotope data was so good with the

tissues studied, it was not considered necessary to repeat earlier determinations on other tissues. The only exception is that the absolute rate of CO oxidation obtained with skeletal muscle by both methods here is somewhat lower than that reported by Stannard (5).

It is concluded from the evidence outlined above that the stimulation of muscle respiration by CO is practically entirely due to its oxidation to CO_2.

Effect of Respiratory Inhibitors on Oxidation of CO. Stannard (5) found that it was possible to prevent the increase in gas consumption of frog skeletal muscle in CO-O_2 mixtures by suitable concentrations of sodium azide and of hydroxylamine. He also showed that this process could be inhibited by concentrations which had no effect on resting metabolism and but little effect on that of stimulated (caffeinized) muscle. A direct measurement of certain of these inhibitor effects by the isotope technique was desired, both for comparative purposes and because in the final analysis the respirometer experiments show only that the *stimulation* is prevented (see next section). The results of experiments comparing respirometer and isotope data (obtained from the same tissues) are collected in table 2.

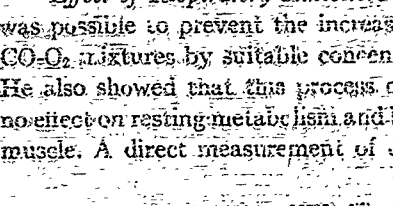

Fig. 1. Comparison of CO burned as measured by volumeter (ordinates) vs. that calculated from isotopic (C^{14}) carbon dioxide produced (abscissae).

The results in table 2 show that the oxidation of CO by muscle is completely prevented by 0.01 M sodium azide and 0.02 M hydroxylamine, and that the data from respirometer and isotope measurements agree reasonably well.

From previous work it is known that these concentrations of azide and hydroxylamine would completely prevent both the stimulation of respiration due to CO and the extra metabolism of stimulated muscle. By contrast it is seen that the gas consumption of the resting muscle in air was unaffected by the hydroxylamine and stimulated by the azide. The latter is explained by the slight contracture produced by azide, and it is interesting to note that this stimulation appears to be sensitive to CO as evidenced by the negative trend of the change in gas consumption when CO is added in the presence of azide. While this presents a slight complication it is clear that the CO oxidation is very low in hydroxylamine and negligible in sodium azide. Because of the effects of these inhibitors on normal metabolism, the isotope data probably represent the more reliable measure of CO oxidation rates.

Effect of CO on 'Normal' Metabolism. It has been thought generally that CO oxidation, if it occurred, was superimposed upon the resting respiration of the tissues, sometimes with some inhibition of normal metabolism (2, 3, 5). No formal study of this phase has been undertaken with the isotope technique but certain pertinent points have appeared in the current results.

It will be noted from the control experiments in table 2 (no inhibitor) that the average rate of gas consumption expected on the basis of the radioactive CO_2 measure-

ment is slightly higher than that actually observed with the respirometer. This suggests that actually slightly *more* CO_2 is burned than is predicted by respirometer experiments and this may be explained on the basis of a slight inhibition of normal metabolism. This is contrary to the conclusion derived from the data of figure 1.

With the thought that there might be some radioactive CO_2 retained within the tissues, which would mean still more CO burned than predicted by the respirometer, the tissues were acidified at the end of the experiment in some cases and the gas collected for analysis. Details of the technique, which was designed to insure collection of all the CO_2 released, are given by Clark (6). In the five analyses made the retention was less than 3 per cent of the total CO_2 from CO oxidation in two of the cases with skeletal muscle and the one measurement on heart. In the other two measurements

TABLE 2. EFFECT OF SODIUM AZIDE AND HYDROXYLAMINE ON CO BURNING BY ISOLATED RESTING FROG SKELETAL MUSCLE IN 80% CO AND 20% O_2. VOLUMETRIC METHOD (RESPIROMETER) COMPARED WITH ISOTOPE (C^{14}). (RINGER-PHOSPHATE AT PH 7.3, 22°C. EXPERIMENTAL PERIOD 5 HOURS[1])

INHIBITOR ADDED	CONC.	RESPIROMETER			ISOTOPE	
		Air[2]	CO_2[2]	Change[2] (= excess gas)	CO burned	Calculated excess gas[2]
None[3]		0.27	0.48	+0.21	0.185	0.278
Sodium azide	0.01 M	0.57	0.36	−0.21	0.00	0.000
Sodium azide	0.01 M	0.59	0.38	−0.21	0.01	0.015
Hydroxylamine	0.02 M	0.28	0.27	−0.01	0.035	0.053
Hydroxylamine	0.02 M	0.26	0.23	−0.03	0.038	0.057

[1] Except for one experiment with no inhibitor which ran 6 hours. [2] mm^3/gram wet weight/min. [3] Average of four experiments.

on skeletal muscle the retention was about 30 per cent. In one of these instances, however, a drop of alkali was spilled and this case should probably be dropped from the series. Assuming the other cases to be reliable there is evidence of a *very slight* additional amount of CO burning not reported in figure 1 and tables 1 and 2. Obviously this does not influence in any way the conclusion that the stimulation is due entirely to oxidation of CO.

DISCUSSION

The experiments described in this paper show by direct analysis of the respired CO_2 using radioactive C^{14} in the CO of the original CO-O_2 mixture that the apparent stimulation of the gas uptake of isolated frog heart and skeletal muscle is entirely due to oxidation of CO to CO_2. There is qualitative and quantitative agreement in the overall picture obtained by the use of isotope techniques with that obtained by respirometry. Tissues such as nerve and skin which failed to show any increase of gas uptake in CO also showed no appreciable radioactivity in the respired CO collected.

These findings confirm and strengthen the conclusions of Fenn and Cobb (1, 2), and of Stannard (5). While various possible alternative explanations for these findings,

particularly those suggested by Haldane and Priestley (10) were shown to be quantitatively inadequate by Stannard (5), it is felt that the present experiments offer final proof for the presence of this oxidative reaction in muscle.

The significance of this reaction in metabolism presents an interesting biochemical problem. We have found that it occurs in the intact animal (11, 12) although the rate is, of course, very much lower than in the experiments recorded here with 80 per cent CO-20 per cent O_2.[4, 5] We do not anticipate that it will be of much significance in the physiological adjustments immediately following exposure to CO or in 'adaptation' to long continued exposure. But the enzyme mechanisms involved and the apparent limitation of the phenomenon to muscle are considered worthy of further study.

SUMMARY

Various tissues of the frog were exposed to 80 per cent CO and 20 per cent O_2 for periods ranging from 5 to 10 hours. The rates of gas consumption in CO-O_2 mixture and in air were measured in a respirometer. The radioactive isotope C^{14} was used in the CO-O_2 mixtures and the amount of CO burned to CO_2 was calculated from radioactivity measurements of the respired CO_2. The amount of CO burned was found to agree with the excess gas consumption in the respirometer thereby showing that the excess gas consumption was due to the burning of CO to CO_2. The rate of CO oxidized by frog tissue was found to be highest for heart muscle, next for skeletal muscle, and negligible in nerve or skin. The amount of CO burned to CO_2 but retained within the tissue was found to be a small fraction of the total CO burned. It appears that the burning is superimposed upon the resting metabolism of muscle tissue with perhaps slight inhibition of the latter. Sodium azide and hydroxylamine completely blocked the oxidation of CO measured by both respirometer and isotope techniques.

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[4] A preliminary report of the present experiment was given at the Minneapolis meetings of the American Physiological Society, October, 1948. Abstract in *Am. J. Physiol.* 155: 430, 1948.

[5] A complete account of the experiments with intact animals is in preparation.

[6] This work is part of a general program supported by The Air Materiel Command, Wright-Patterson Air Force Base. The C^{14} experiments were conducted in part under contracts between the U. S. Atomic Energy Commission and the Office of Naval Research with the University of Rochester.

EVIDENCE FOR CONVERSION OF CARBON MONOXIDE TO CARBON DIOXIDE BY THE INTACT ANIMAL

ROBERT T. CLARK, JR.

INDIRECT evidence that the stimulating effect of carbon monoxide on the respiration of certain isolated tissues was due to the oxidation of carbon monoxide to carbon dioxide was first presented by Fenn and Cobb (1, 2). Their conclusions were based on a comparison of total gas consumption, measured by a respirometer, with the oxygen which disappeared, as determined by gas analysis of the respirometer contents before and after the period of respiration of the tissues. Subsequent investigators (3–5), also by indirect methods, confirmed these findings. Recent experiments (6), involving the use of the radioactive isotope C^{14}, and based upon the calculation by radioactivity measurements of the amount of carbon monoxide burned to carbon dioxide in intact tissues, gave direct results which agree with those found by the indirect methods.

The experiments involving isolated tissues were carried out in an atmosphere containing about 80 per cent CO in oxygen. No experimental data indicated the ability of an intact animal to make the conversion at low CO concentration. Campbell (7) tried the experiment with rabbits, but at that time the methods for measuring CO were not sufficiently accurate to prove the point one way or the other. Tobias *et al.* (8), using the short-lived C^{11}, and Killick (9), using a rebreather circuit, found that negligible amounts were burned in experiments on the human body. Their experiments, lasting approximately forty minutes, do not preclude the possibility of CO oxidation by the intact animal in experiments covering a much longer period of time. In the present study, therefore, an attempt has been made to determine the response of mice and turtles to small concentrations of CO over periods of time ranging from two to ten days. Two methods of approach have been used: *a*) gasometric measurement of the CO disappearing from a closed chamber, using the Roughton and Root technique (10), and *b*) collection of the expired CO_2 from animals residing in an atmosphere containing CO, some of which was the radioactive $C^{14}O$, and measurement of its radioactivity by the method of Baie *et al.* (11).

EXPERIMENTS WITH TURTLES

Methods. The apparatus used for the experiments consisted essentially of a 60-liter aquarium, a 15-liter spirometer, and a check-valve system. The top of the aquarium was sealed by means of a lucite cover that was lined around the under

edge with sheet rubber, thereby making an air-tight lid when secured to the aquarium by means of vacuum grease. In addition, the lid was firmly fastened by placing 4 iron bars across the top of the aquarium. The bars were attached on each side to turn-buckles which were adjusted so as to cause the springs to exert a steady tension upon the bars, thus insuring a tight seal to the aquarium at all times during the experiment. A rubber stopper with a 3-way stop-cock was inserted into an opening at one end of the lucite cover, and a metal T-tube at the other end. One arm of the T-tube was attached to a water manometer and the other, by way of a one-way check valve system, to a spirometer. The check valve system consisted of a thistle tube, mercury, and half of a ping-pong ball.

The turtles were placed on the floor of the aquarium and enough soda lime was added to a pan above the animals to absorb all the CO_2 for approximately two weeks. As the CO_2 was absorbed a slight negative pressure was formed within the aquarium, thereby lifting the ping pong ball and pulling over sufficient pure oxygen to replace that used by the animals.

Commercial CO was used in all the experiments. In order to add CO, the connection to the spirometer was first clamped off, and with the aid of a syringe the same amount of gas was removed from the aquarium that was to be replaced with CO. From 10 to 12 hours was allowed for the CO to become thoroughly mixed with the other gases in the tank. Also, this interval of time was considered adequate for the CO to be taken up by the blood stream and tissues of the animals, as well as to reach equilibrium with the soda lime. Samples for analyses were taken initially, after the equilibration period of 10 to 12 hours, and then either daily or at the end of the test period. For the control experiments, the food, accumulated feces and urine, and soda lime were left in the aquarium at the end of the experimental period and CO determinations were made without the animals present. The analyses were carried out according to the sensitive technique described by Roughton and Root (10). This method was found to check satisfactorily against other sensitive methods in which entirely different techniques were followed.[2]

Results. Table 1 shows the amount of CO lost from a 60-liter aquarium, as measured by the gasometric method of Roughton and Root in 5 experiments with turtles. The table shows that in all cases considerably more CO disappeared in the presence of the turtles than in the control period. The rate of burning in the control period was either very small or was lacking altogether. From 30 per cent to 52 per cent of the CO present was consumed by the animals at the concentrations given in table 1.

The rate of change of CO in the presence of the turtles showed a slow but steady decrease during the experimental period.

EXPERIMENTS WITH MICE

Oxidation of CO Measured by Gasometric Technique: Methods. The set-up for the mice was essentially the same as for the turtles. It consisted of a spirometer and a

[2] Many thanks are due the Chemistry Division, Rochester Gas and Electric Corporation, Rochester, N. Y., for their cooperation in analyzing some of our samples as a check against the method used by us. Also we wish to thank the Department of Gas Chemistry, Bureau of Standards, for furnishing us with a CO-air mixture analyzed by their method.

similar check-valve system, but a different sort of container for the animals. The container consisted of a 12.5-liter desiccator equipped with a water bottle, thermometer, and connections for the spirometer and mercury manometer, the latter also being attached to a T-tube in order that gas samples could be added or removed from the desiccator. The mice were allowed to move around on a perforated, porcelain floor of the desiccator, below which was placed the soda lime. Enough food was added to last for the duration of the experimental period.

The procedure for carrying out the experiments was the same as for the turtles. The CO concentration was first determined after a 10- to 12-hour equilibration period and again at the end of the [illegible]. Analyses were made by the Roughton and Root technique. The [illegible] ated the experimental except for the absence of the ani[illegible]

Results. Table [illegible] s with mice in which the amount of CO burn[illegible] ermined by measuring [illegible] in CO concentration with and witho[illegible] nount of CO lost with [illegible] as cor-

TABLE I. DISAPPEARANCE FROM CLOSED CHAMBER (60 LITERS) WITH AND WITHOUT TURTLES
Experiments; Values Expressed at STP

EXPER.	TIME[1]	Init. CO	AMOUNT CONSUMED		
			With Turtles	Control	Diff.
	days		*ml.*	*ml.*	*ml.*
1	8	[illegible]	5.92	0.00	5.92
2	7	[illegible]	7.71	1.20	6.51
3	13	[illegible]	12.03	2.68	9.35
4	11	[illegible]	14.86	1.08	13.78
5	10	[illegible]	13.30	0.00	13.30

[1] Number refers to dur[illegible] of *each* p[illegible]l, control and experimental.

siderably more than t[illegible]ost du[illegible]g the 4-day control period at the end, thu[illegible] dicating that in some [illegible]e were consuming the CO. The data indi[illegible] disappearance of CO a[illegible]e ap[illegible]ximately 0.24 cu. mm./gm. body wt/hr.

Oxidation of CO [illegible]ioactive C[illegible] Methods. The apparatus used wa[illegible] essentially the same as [illegible]sly described. The mice were placed in a 500-cc. beaker within the des[illegible]t[illegible] enough food for 3 days. Approximately 80 gm. of NaOH was placed [illegible] Erlenmeyer flask and 100 cc. of distilled water added to dissolve the a[illegible] tube was attached to the spirometer connection and extended on into [illegible] By this means pure oxygen from the spirometer was forced to bubble t[illegible] [illegible]kali before entering the desiccator, thus preventing a complete layer of [illegible]m forming [illegible] the surface of the NaOH.

The C[illegible] labeled C[illegible]ared by release of CO_2 from $BaCO_3$ having a specific activity of 384 [illegible] [illegible] was reduced to CO after the method of Bernstein and Tayl[illegible] [illegible]d for use according to the method described in a previous [illegible] [illegible]e experimental period the Erlenmeyer flask containing [illegible] [illegible] radioactive measurements were

made with the CO_2 in gaseous form (12). After the mice were removed a fresh solution of NaOH was placed in the desiccator and a control run was carried out in exactly the same manner as the experimental.

Results. The results of the two experiments are summarized in table 3. There was very little radioactivity in the CO_2 obtained in the control periods compared to the high activity of the CO_2 collected in the presence of the mice. After correction for the activity of the controls, due probably to solution of CO plus conversion to formate, the remainder gives a measure of the CO oxidized to CO_2 by the mice. The figures indicate disappearance of CO at a rate of about 0.28 cu. mm/gm/hr. The results obtained by this method give the same values as those listed for CO consumption by the gasometric method, therefore indicating that the CO consumed by the mice in the first group of experiments was due to the burning of CO to CO_2.

TABLE 2. DISAPPEARANCE OF CO FROM CLOSED CHAMBER (12.5 LITERS) WITH AND WITHOUT MICE

Gasometric Experiment, Values Expressed at STP

TIME	TOTAL WT. OF MICE	INITIAL CO CONCEN.	AMOUNT CONSUMED		RATE OF LOSS
			With Mice	Control	
days	*gm.*	*%*	*ml.*	*ml.*	*cu. mm/hr.*
4	246	0.071	4.49	0.13	0.20
4	294	0.080	8.16	0.84	0.26

TABLE 3. CONVERSION OF CO TO CO_2 BY MICE

Experiment with Radioactive Carbon Monoxide ($C^{14}O$)

TIME	TOTAL WT. OF MICE	INITIAL CO CONCEN.	ACTIVITY MEASUREMENTS OF $C^{14}O_2$ COLLECTED			RATE OF CONVERSION
			With Mice		Control	
days	*gm.*	*%*	*d/min. × 10⁻⁵*	*sp. activity mc/gm. carbon*	*d/min. × 10³*	*cu.mm/gm/hr.*
2.67	57	0.07	459	0.06	0.63	0.28
2.00	47	0.07	306	0.052	2.54	0.29

While the specific activities in the collected CO_2 are low compared to the original CO, actually for each gram of carbon present as CO in the chamber, 22.7 per cent and 19.3 per cent, respectively, were converted to CO_2 in the two experiments.

DISCUSSION

Our present results in no sense contradict those of other investigators, since they were carried out under entirely different conditions. Our results indicate that CO is burned by mice at a rate 10 times greater than would be expected by a straight

Experiments with radioactive C^{14} in this paper were conducted in part under a contract with the U. S. Atomic Energy Commission at the University of Rochester Atomic Energy Project, and another between the Office of Naval Research and the University of Rochester. The cooperation of Drs. W. F. Bale, R. W. Reinkamp and their assistants is gratefully acknowledged. This work is part of a program supported by the Air Materiel Command, Wright Field.

line extrapolation from results [illegible] per cent oxygen (6). The rate of [illegible] corded because the control e[illegible] mental period. Therefore, the [illegible] some CO to CO_2 were conceivably [illegible] perimental period and might [illegible] time, whereas an experimental [illegible]

If the rate of burning observed [illegible] would expect approximately [illegible] per cent. This is almost 30 [illegible] Tobias *et al.* in their experiments. [illegible] metabolic rate, then the rate of [illegible] ably greater than that by man.

Turtles were exposed in a [illegible] riods ranging from 8 to 13 days. [illegible] the container during the period, [illegible] 30 per cent to 52 per cent of the CO.

Mice were similarly exposed to [illegible] drop in CO concentration during this [illegible] CO at the rate of 0.[illegible] cu. mm/gm [illegible] the radioactive isotope C^{14} was used [illegible] activity of the respired CO_2 showed [illegible] rate of 0.28 cu. mm/gm/hr. This [illegible] ments with mice and turtles, [illegible] due to the burning of CO to CO_2 [illegible] was 10 times greater than would be [illegible] isolated muscle in 80 per cent CO [illegible]

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