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ABSTRACT

Title of Dissertation: The effect of gas density on gas transport during high frequency oscillation.

Elizabeth J. McCarthy, Doctor of Philosophy, 1985 Dissertation directed by: John R. Clarke, Ph.D., Adjunct Professor Department of Physiology

High frequency oscillation (HFO) is a ventilatory technique which applies tidal volumes less than dead space to the airways at frequencies of 2-50 Hz. Potential benefits have been reported for the clinical use of HFO, especially for premature infants with respiratory distress syndrome. Because of the small tidal volumes, the classical methods for measuring ventilation do not apply during HFO. Several theories have been proposed to explain the mechanism of gas transport but there is presently no general concensus as to the primary mechanism responsible for gas transport during HFO.

Previous studies of both conventional ventilation and normal breathing found no effect of inspired gas density on PaO_2 or $PaCO_2$. The purpose of the present research was to determine the effect of gas density on gas transport during HFO to provide additional insight into the mechanism of gas transport.

In the present studies HFO was delivered to dogs via an endotracheal tube using an Emerson piston pump oscillator with a frequency range of 12-34 Hz and a tidal volume range of 20-30 ml. Anesthetized dogs were ventilated with HFO at 30 Hz using either 80% He-20% O_2 or 80% SF_6-20% O_2 at equal flow rates. By shunting various fractions of the ventilator stroke volume during gas density changes, chest wall motion was maintained constant as measured by an accelerometer placed on the chest wall.

In different studies the transport of oxygen, carbon dioxide and halothane were measured during HFO with the two gas mixtures.

These studies showed that gas density affects gas transport. The results indicated that effective ventilation as measured by an increase in PaO_2 and arterial halothane, and a decrease in $PaCO_2$ improved with the more dense gas mixture, SF_6-O_2.

In contrast to conventional ventilation, gas exchange during HFO is dependent on gas density in the airways. The efficiency of gas exchange with HFO increases as gas density increases with concomitant decreases in kinematic viscosity and molecular diffusivity. These data agree with the theoretical analyses of gas transport with HFO by Fredberg (1980) and Kurzweg et al. (1984).

THE EFFECT OF GAS DENSITY ON GAS TRANSPORT DURING HIGH FREQUENCY OSCILLATION

by

Elizabeth J. McCarthy

Dissertation submitted to the Faculty of the Department of Physiology
Graduate Program of the Uniformed Services University of the Health Sciences
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy 1985

DEDICATION

I dedicate this dissertation to Mr. George P. Emerson, the inventor of the high frequency oscillator which was used on all of my studies and, to Dr. Robert L. Watson who facilitated the loan of this ventilator to do the physiologic studies which I will present.

ACKNOWLEDGEMENTS

I wish to thank Dr. John Clarke for his unfailing guidance throughout my research studies with high frequency oscillation.

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BACKGROUND

High frequency oscillation (HFO), the application of small tidal volumes at high frequencies, is a new ventilation technique being investigated for clinical application. HFO has already been clinically applied in both adults (Butler et al., 1980; Rossing et al., 1981; Crawford and Rehder, 1985) and in infants (Marchak et al., 1981; Frantz, et al., 1983). Its advantages over conventional ventilation techniques include lowered airway pressures and improved gas transport. Unfortunately, the mechanism of gas exchange with HFO is not well understood and there are few guidelines for determination of such variables as frequency, tidal volume, airway pressures, and lung volumes.

West (1981) described the following relationship for ventilation of an adult for normal breathing:

$$\dot{V}_A = (V_t - V_d) \cdot f \qquad [1]$$

where f is the respiratory frequency, $\dot{V}_A$ is alveolar ventilation, V_t is tidal volume and V_d is dead space volume. The classical method for determining ventilation does not apply with HFO because tidal volume, as defined by Slutsky et al. (1980), is less than dead space.

Traditional concepts of pulmonary physiology are challenged by HFO. Tidal volume in an adult is approximately 500 ml, much larger than dead space volume. The respiratory rate at this tidal volume is approximately 14 breaths per minute. With normal breathing and conventional positive pressure ventilation, pulmonary gas exchange is primarily dependent on convective flow of gases in the large airways. In contrast, tidal volumes in our studies of HFO are less than anatomical dead space and produce effective gas exchange at frequencies up to 34 Hz (Hz = 1 cycle$\cdot$sec^{-1}).

In 1959 Emerson, a manufacturer of ventilatory-support equipment, patented a device to "vibrate the column of air in a patient's lung." In the patent Emerson (1959) stated that such vibrations would enhance and promote gas mixing. Although he provided no experimental evidence to substantiate this, many subsequent clinical reports support the efficacy of this approach to ventilation and gas exchange (Butler et al., 1980; Marchak et al., 1981; Smith., 1982; El Baz et al., 1983). Bland et al., (1980) reported that rapid ventilatory frequency provided adequate support to human neonates with respiratory distress syndrome. Butler et al., (1980) reported that high frequency oscillation decreased pulmonary shunt fraction in both adults and neonates with ventilation-perfusion mismatch. Marchak et al., (1981) reported that high frequency oscillation increased mean airway pressure resulting in improved oxygenation and decreased peak airway pressure diminishing lung barotrauma in neonates with respiratory distress syndrome.

Research on the physiological mechanism of gas exchange with high frequency oscillation has been less extensive than clinical research due to the technical difficulty in measuring ventilation parameters using this technique. Several groups (Lunkenheimer et al., 1973; Bohn et al., 1980; Slutsky, et al., 1980; Schmid, et al., 1980; Goldstein, et al., 1981; Rossing, et al., 1981) have reported that frequencies up to 40 Hz with oscillatory volumes of 1-3 ml/kg in dogs can provide adequate gas exchange. Lunkenheimer et al. (1972, 1973), first in a letter and the following year in a full report reported using a ventilator with a frequency dependent stroke volume of 10-30 ml with an optimum frequency of 40 Hz through a tracheal tube to initiate vibrations in the thoracic cage of anesthetized dogs. The total period of vibration was 40 minutes. The CO_2 elimination was directly related to

frequency changes and amplitude of vibrations as measured by esophageal pressure. The dogs survived without respiratory insufficiency. Lunkenheimer et al., (1972) saw the application of transtracheal oscillations as an advantage for thoracic surgery because of decreased motion of the lungs due to ventilation.

Bohn et al. (1980) used a piston pump oscillator with variable frequency (5-30 Hz) and tidal volume (1.7-2.3 ml/kg) to ventilate dogs. A piston displacement of 1.9 ml/kg, a volume less than dead space, was required to obtain a P_aCO_2 value of 33.1 ± 0.5 mm Hg (mean ± SE). Peak airway pressures were measured at 4-8 cm H_2O. With this system the optimum ventilation frequency was 15 Hz. This optimum frequency was not in keeping with the findings of others (Ngeow et al., 1980; Slutsky et al., 1980; Schmid et al., 1981; McCarthy et al.,1983). Using an Emerson oscillator with a stroke volume of 90 ml and frequency range of 1-32 Hz, Ngeow et al. (1982) found as frequency increased $PaCO_2$ decreased with an optimal frequency of 20 Hz.

Fredberg (1980) applied Bohn's data to a theoretical model to demonstrate that augmented diffusion in the central airways combined with molecular diffusion at the alveolus can account for most pulmonary gas transport in HFO. Slutsky et al. (1980) further noted the significant variable in HFO to be the amplitude of the oscillatory flow independent of frequency and stroke volume. Flow was measured with a pneumotachometer which was calibrated prior to all experiments with a piston pump driven in the range of 3-30 Hz with a stroke volume varying from 20 to 100 ml. In four dogs (8-22 kg) using frequencies of 4-30 Hz and stroke volumes 20-85% of calculated dead space, results showed as frequency increased at fixed stoke volume gas transport increased as measured

by CO_2 output. He concluded that if frequency is high enough to maintain tracheal flow effective gas exchange would be produced.

Enhancement of pulmonary gas exchange due to the physiologic oscillations of the heart as they affect the lungs has also been investigated. Fukuchi et al. (1976) performed in vivo studies in dogs to show that action of the heart enhances gas mixing and the effective diffusion of gas is greater than can be accounted for by molecular diffusion. Using an N_2 washout technique, the mouthward N_2 transport due to mixing in vivo in the presence of cardiogenic oscillations was calculated to be 5.6 times greater than the diffusion of nitrogen in post mortem dogs. Thus, Fukuchi et al., (1976) showed that gas mixing in the airways is accelerated by the oscillations caused by the heartbeat.

Schmid et al., (1981) examined the effects of HFO on the pulmonary ^{133}Xe clearance after right atrial bolus injection during HFO at 16 and 30 Hz in six anesthetized dogs using a stroke volume of 2.6 ml/kg. They found the mean clearance rate of ^{133}Xe was statistically faster at 30 Hz than at 16Hz. Measurements of PaO_2 and $PaCO_2$ showed more effective ventilation at 30 Hz. Their results showed a more uniform clearance of ^{133}Xe during HFO compared to conventional ventilation. These studies also found intraregional mixing of ^{133}Xe occurred during HFO and tended to be greater at the higher frequency. These studies indicate an increase in intraregional gas mixing and decreased $PaCO_2$ at increasing frequencies.

The effect of gas density on gas transport has been studied extensively with conventional ventilation. Worth et al., (1976) examined the effect of inspired gas density on gas transport and ventilation. No significant difference in gas transport or ventilation as measured by $PaCO_2$ or PaO_2 was found in dogs ventilated with inspired gases of 80% helium (He), 20% oxygen

($He-O_2$) and 80% sulfurhexafluoride (SF_6) 20% oxygen (SF_6-O_2) at constant tidal volume and frequency. These observations were confirmed by Wood et al., (1976) and Christopherson and Hlastala (1982). In these studies tidal volume delivered did not change when gas density was changed, and adjustments in the stroke output of the ventilator were not necessary.

At ordinary respiratory frequencies in resting adult humans, tidal volume is distributed among lung regions on the basis of local compliance (LaForce, and Lewis 1970; Martin, et al., 1972; Sikand et al., 1976; Paiva and Engel, 1979). With HFO, inspired gas density affects airway impedence between the mouth and alveoli. When gas density is changed tidal volume cannot be directly measured or deduced from flows at the mouth because changes in impedence along the airways change tidal volume delivered to the alveoli. Resistance, compliance, and inertance are involved in airway impedence in the following relationship:

$$Z_T = Z_R + Z_I + Z_C \qquad [2]$$

where Z_T = total impedence, Z_R = resistive impedence Z_I = impedence of inertance, and Z_C = impedence of compliance. Conventional ventilation has low frequencies, large tidal volumes, and Z_R is the major component of its total impedence. Resistive impedence is determined primarily by friction in the airway and is defined as the pressure difference needed for steady flow. Inertance is determined by inertia which is defined as the resistance offered by a body to a change of its state of rest or motion. Impedence due to inertance becomes important at the high frequencies used with HFO because it is proportional to the angular velocity times the inertance. Angular velocity is determined by frequency (angular velocity = $2\pi f$) and inertance is directly proportional to gas density. Therefore, as frequency increases inertance becomes a more significant part of total impedence. On the other hand,

impedence due to compliance (Z_C) of the airway gases, airways and lung tissue is inversely proportional to frequency. Thus, as frequency increases, Z_C becomes a less significant part of the total impedence. Because impedence due to inertance rises with an increase in gas density, measurements of ventilator stroke volume and volume at the mouth cannot be interpreted as measurements of alveolar tidal volume during HFO when inspired gas density changes. Brusasco et al., (1983) reported an effect of impedence by measuring the pulmonary wash-in rate of a tracer gas, ^{133}Xe, with HFO at frequencies of 1-60 Hz in dogs. He found that HFO stroke volume was not the same as the delivered gas volume with SF_6-O_2 at frequencies of 30 Hz or greater. At frequencies higher than 30 Hz with SF_6-O_2 his ventilator was unable to adequately ventilate.

Impedence changes can be measured by airway pressures, airway flows, or chest wall acceleration. During oscillatory flow at a constant frequency, if volume displacement increases acceleration will increase linearly. Thus, acceleration can be used as an estimate of volume displacement during HFO. In our experiments tidal volume was estimated by measuring chest wall displacement on dogs ventilated with HFO using an accelerometer to account for changes in impedence with changes in gas density.

Existing hypotheses of Fredberg (1980) and Kurzweg et al., (1984) about the mechanism of gas transport with HFO involve references to physical properties of gases in the airway which are changed when gas density changes. These physical properties include not only density, but also viscosity, kinematic viscosity which is viscosity divided by density, and molecular diffusion.

Diffusion and turbulence are inversely affected by these physical properties. Diffusion, the net transport of material within a single phase in the absence of mixing by mechanical means or convection, is inversely

proportional to the square root of the molecular weight (Reid et al., 1977). Respiratory physiologists generally recognize that molecular diffusion contributes to the transport of oxygen and carbon dioxide in the gas phase near the alveolocapillary membrane. Gas transport due to diffusion is inversely proportional to density and the molecular weight of the inspired gas.

According to Slonim and Chapin (1967), Reynolds found that the transition from laminar to turbulent flow is dependent upon flow velocity, tube radius, gas density, and gas viscocity. He combined these variables to produce the following equation:

$$Re = v \times 2r \times \rho / \eta \qquad [3]$$

where Re is Reynold's number, v is the average linear gas velocity, ρ is density of the flowing gas, and η is gas viscosity. If consistent units are used, Re is dimensionless. For Newtonian fluids when Re is less than 2,000 flow tends to be laminar in straight tubes, and when Re is greater than 2,000 it tends to be turbulent. During normal quiet respiration, gas flow is laminar in the bronchioles and small airways, turbulent in the larger airways, and transitional, neither laminar nor fully turbulent, in the majority of the airway generations. Fredberg (1980) was the first to suggest that turbulent dispersion was responsible for the success in ventilation during HFO. He states that the flow of gases with HFO is turbulent, produces lateral mixing, and the importance of axial diffusion is minimal except at the alveolocapillary membrane. According to the model of Fredberg, with an increase in Reynold's number gas transport would increase.

Another description of gas transport has been described by Jaeger and Kurzweg (1983) based on experimental measurements of the longitudinal dispersion coefficient (D/D_m) with oscillating flow in pipes of binary gas

mixtures at high oscillation frequencies. Their experimental data were described by the following relation:

$$D/D_m = 1 + 0.075\ \Delta x^2 \cdot f/\nu \qquad [4]$$

where Δx = tidal displacement, f is the oscillation frequency and ν, kinematic viscoscity, is approximately inversely proportional to gas density. Kurzweg, Howell, and Jaeger (1984) developed another model for measurement of enhanced dispersion in oscillatory flows in pipes using a wide range of tidal displacements and tube radii. In this model the dispersion coefficient was found to be a function of the Womersley number (α). Womersley squared is defined as:

$$\alpha^2 = f \cdot r^2 (2\pi/\nu) \qquad [5]$$

where f is frequency, r is radius, and ν is kinematic viscosity. This model predicts that as kinematic viscosity decreases the dispersion coefficient, and therefore gas transport, increases. To test the two models, Jaeger and Kurzweg employed a wide range of frequencies with different tube radii, but did not change gas density or kinematic viscosity.

The object of the present studies is to expand the testing of the models of Fredberg (1980) and Kurzweg et al., (1984). Instead of using tubes, the present studies will use dogs which are a better simulation of the physiologic state to measure gas transport. To qualitatively test the above models, frequency and displacement were varied and dispersion coefficients, an index of gas transport were measured. To further test these models, kinematic viscosity, density and molecular diffusion will be varied by changing gas density and gas transport will be measured.

RATIONALE

The objective of our studies is to determine the effect of gas density during HFO on gas transport. In these studies, to correct for changes in effective tidal volume due to impedance, tidal volume will be approximated at the chest wall using an accelerometer, and the stroke output of the oscillator will be varied during gas density changes to maintain equivalent tidal volumes. With frequency and tidal volume, equivalent inspired gas density will be changed and measurements similar to studies by Worth et al. (1976) with conventional ventilation will be performed.

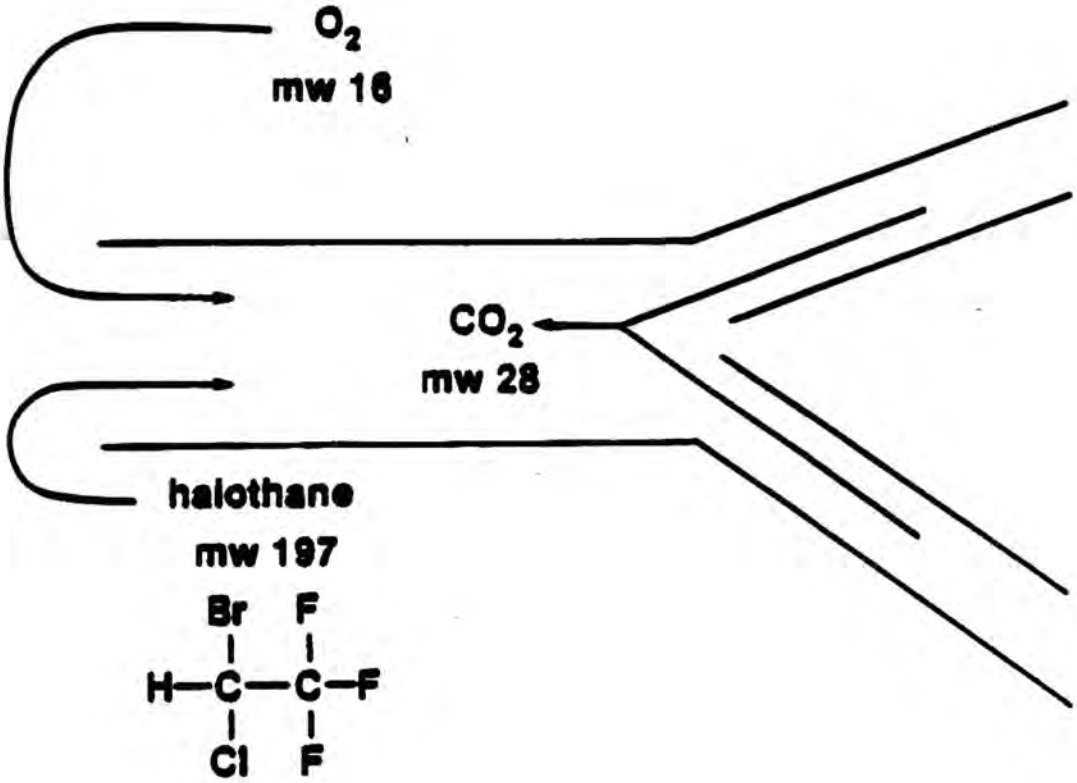
In these studies the following gases will be used as an index of gas transport with HFO when inspired gas density is changed: arterial blood oxygen (P_aO_2), carbon dioxide (P_aCO_2) and halothane. As shown in Figure 1, oxygen and halothane are transported through the airways to the arterial blood and carbon dioxide is transported out of the arterial blood exiting from the upper airway. As ventilation increases, arterial halothane and oxygen is augmented and arterial carbon dioxide is reduced. The equations for gas exchange and effective alveolar ventilation for carbon dioxide and oxygen are as follows:

$$P_ACO_2 = (P_B - 47\text{mmHg})\ (F_iCO_2 + \dot{V}CO_2 / \dot{V}_{Ae}) \qquad [6]$$

$$P_AO_2 = (P_B - 47\text{mmHg})\ (F_iO_2 - \dot{V}O_2 / \dot{V}_{Ae}) \qquad [7]$$

where P_ACO_2 and P_AO_2 are alveolar concentrations of carbon dioxide and oxygen respectively, P_B is the barometric pressure, F_iCO_2 and F_iO_2 are inspired fractions of CO_2 and O_2 respectively, $\dot{V}CO_2$ and $\dot{V}O_2$ are the CO_2 production and the O_2 consumption respectively, and $\dot{V}_{Ae}$ is effective alveolar ventilation. Given this relationship between effective alveolar ventilation and alveolar gas tensions one can use these two gases as markers for measuring ventilation and effective gas exchange. According to Nunn (1969), for all practical

Figure 1. A schematic of the direction of transport in the airways of the three gases, oxygen (O_2), carbon dioxide (CO_2), and halothane, used to measure gas transport with high frequency oscillation. MW = molecular weight.


O_2
mw 16
CO_2
mw 28
halothane
mw 197
Br F
H—C—C—F
Cl F

purposes, alveolar PCO_2 is equal to arterial PCO_2 in healthy animals. Therefore, there is a decrease in arterial CO_2 when alveolar ventilation and gas exchange increase. Arterial oxygen and ventilation-perfusion distribution will increase when gas exchange increases.

Measurements of these three gases will be taken in the arterial blood as oppposed to measuring their concentrations in the expired gas. The end tidal concentration of a gas is an approximation of the alveolar concentration because with each tidal volume alveolar gas is expired with conventional ventilation. With HFO tidal volumes are less than dead space thus end tidal volume would not necessarily be a measurement of alveolar gas concentration. Furthermore, another source of error may be introduced with this measurement because with HFO the expired gas concentration is dependent on not only effective ventilation but also on the fresh gas flow rate. With an increase in the fresh gas flow rate there would be a decrease in the measured gas concentration in the expired gas due to dilution. Arterial blood concentrations of gases are estimations of alveolar concentrations of gases also, but this measurement does not appear to be dependent on the type of ventilation used. For these reasons, in the present studies the measurement of these three gases will be made by measuring their concentrations in the arterial blood.

Mapleson (1962) administered halothane with spontaneous ventilation at a constant inspired halothane concentration and measured ventilation and uptake of halothane. He found that as alveolar ventilation increased the rate of uptake of halothane increased. Papper and Kitz (1963) used conventional positive pressure ventilation to show that alveolar uptake and concentration of halothane is directly proportional to alveolar ventilation. The increase in the alveolar and arterial concentration of halothane seen with an increase in alveolar ventilation is due to the increase in halothane delivery.

The majority of HFO studies (Bohn et al., 1980; Goldstein et al., 1981; Robertson et al., 1982) have used PaO_2 and $PaCO_2$ as tools for measuring gas exchange and ventilation. Both of these gases are dependent on total body metabolic rate which can easily vary. An alternative to measuring gas transport with PaO_2 and $PaCO_2$ is to use halothane, a high molecular weight anesthetic, as a marker of ventilation. Various multicompartmental models have been developed to measure changes in ventilation with halothane uptake during conventional ventilation (Eger, 1976; Fukui and Smith, 1981a; Fukui and Smith, 1981b). Halothane will be used in addition to blood gases for measuring gas transport with HFO because (1) the alveolar uptake of halothane is not as dependent on the metabolic rate as are PaO_2 and $PaCO_2$, and (2) due to its large molecular weight, halothane extends the upper range of diffusivities to be used during HFO. This range includes the diffusivity of halothane in SF_6-O_2, the gas mixture of least diffusivity and greatest density, and the diffusivity of oxygen in He-O_2, the gas mixture of greatest diffusivity and least density. These combinations of gas mixtures allow the measurement of gas transport with HFO over a range of gas diffusivity.

Results from these studies will demonstrate the effect of gas density on gas transport and ventilation with HFO and possibly provide insight into the mechanism of gas transport with HFO. In addition, by determining the effect of gas density, this work will demonstrate whether the gas density dependence with HFO differs from that of conventional ventilation.

METHODS AND MATERIALS

HFO Ventilator

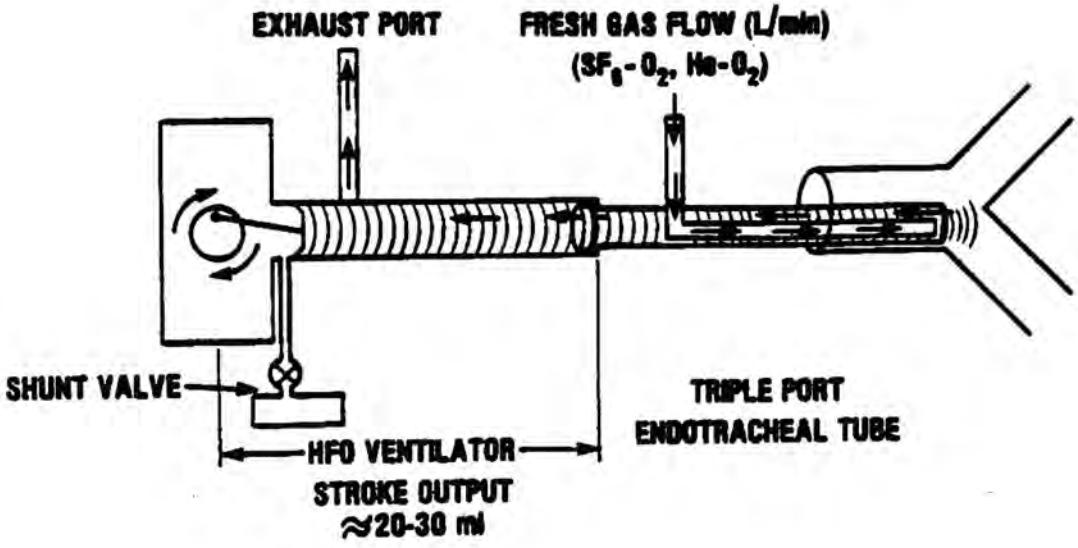
HFO was administered with an Emerson ventilator (Emerson Co., Boston, MA) that displaces a 20-30 ml stroke volume with a piston driven pump which delivered sinusoidal oscillations at frequencies of 12-35 Hz (Figure 2). This HFO device is similar to those used by others to investigate HFO (Keefe, et al, 1981; Slutsky et al, 1981; McEvoy et al, 1982; Banzett et al, 1983). During all gas density studies a frequency of 30 Hz was used because it was the highest frequency at which both gas mixtures could be administered. Because of the increase in impedence placed on the piston pump motor of the oscillator in the presence of SF_6, the maximum frequency with this gas mixture was 30 Hz. All other studies were done at a frequency range of 12-35 Hz. A shunt valve between the piston pump and the oscillatory output tube allowed for a variable ventilator stroke output. By changing the stroke output with this valve, significant chest wall motion changes were prevented during gas density changes.

Accelerometer

Effective tidal volume is dependent on airway impedence which is affected by inspired gas density, especially at high ventilatory frequencies. One way to estimate effective tidal volume with HFO is to measure chest wall movement resulting from applied oscillations. This was accomplished by measurement of chest wall acceleration during all studies involving changes in inspiratory gas density.

Chest wall acceleration was measured with a piezoelectric crystal accelerometer (M117; Wilcoxon Research, Bethesda, MD) fixed to the shaven skin of the lateral rib cage at approximately the 5th intercostal space 4 cm from midline using a spray (3M Adhesive 75 Spray, St Paul,

Figure 2. Schematic diagram of the Emerson HFO ventilator. Frequency range of the ventilator was 12-35 Hz. Oscillatory stroke output delivered to the large lumen of the triple port endotracheal tube was varied by shunting a portion of the stroke volume away from the endotracheal tube. Gas mixtures of different density were delivered through a small lumen of the endotracheal tube to the carina. Gases expired from the animal through the high oscillatory impedence exhaust port.


EXHAUST PORT
FRESH GAS FLOW (L/min)
(SF_6-O_2, He-O_2)
SHUNT VALVE
TRIPLE PORT
ENDOTRACHEAL TUBE
HFO VENTILATOR
STROKE OUTPUT
≈20-30 ml

MN) and tape adhesive. The crystal between the two electrodes is affixed to the base of the accelerometer (Figure 3). Motion of the chest wall generated a force to the accelerometer. This force distorted the crystal lattice emitting electrons causing a voltage change. Thus, the crystal transduced the mechanical energy of the chest wall motion into an electrical signal and acceleration was measured.

The accelerometer was connected to a vibration amplifier (Model PA89; Validyne, Northridge, Cal) and a Fast Fourier Transform (FFT) analyzer (Model 660A; Nicolet Scientific, Princeton, NJ) that displayed ensemble averaged root mean square (RMS) spectra (RMS amplitude vs frequency). The analyzer frequency range was 0-100 Hz. The ensemble was composed of eight four-second samples of acceleration data.

The accelerometer was calibrated before the series of experiments by attaching it to a motor-driven piston with known frequency and amplitude displacement and the output was recorded by the FFT analyzer (Table 1). The calibration range contained the range of accelerations measured in the series of experiments. Assuming sinusoidal motion acceleration was calculated and expressed in g, the acceleration due to gravity. The standard value for g is 32.174 $ft \cdot sec^{-2}$ (Weast and Astle, 1982). The assumption of sinusoidal motion was tested by determining the ratio of the RMS amplitude at the first harmonic frequency to the amplitude at the fundamental frequency. The ratio was less than .01 which is within the acceptable limits for sinusoidal motion. The calibration data for the accelerometer is presented in Table 1 and Figure 4. With sinusoidal motion, as acceleration increases displacement increases linearly if frequency is constant because of the following relationship:

$$\text{Displacement} = k \cdot a \quad f^{-2} \qquad [8]$$

Figure 3. Schematic of piezoelectric-crystal accelerometer. A crystal between two metallic electrodes was mounted on a base and fastened to the chest wall of a dog. The mass exerted a force on the crystal generating voltage which is proportional to acceleration.

PIEZOELECTRIC CRYSTAL

ACCELEROMETER

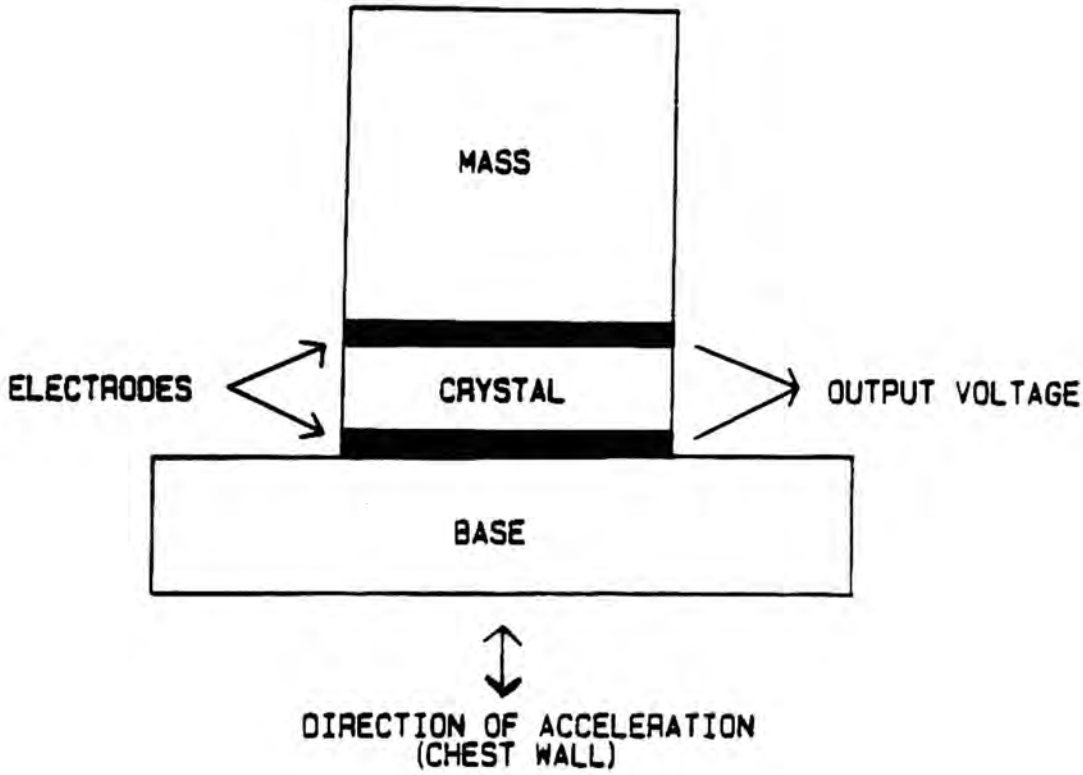


Table 1. Calibration of the Accelerometer Using a Piston with Known Frequency and Displacement

$$\text{Displacement (in)} = 19.59\ a \cdot f^{-2}$$

Frequency (Hz)	Displacement (in)	Calculated Acceleration (a)	FFT Reading (mV)
5	.5	0.64 g	109
10	.5	2.56 g	451
15	.5	5.75 g	1025
20	.5	10.22 g	1855
21	.5	12.23 g	2140

in = inches

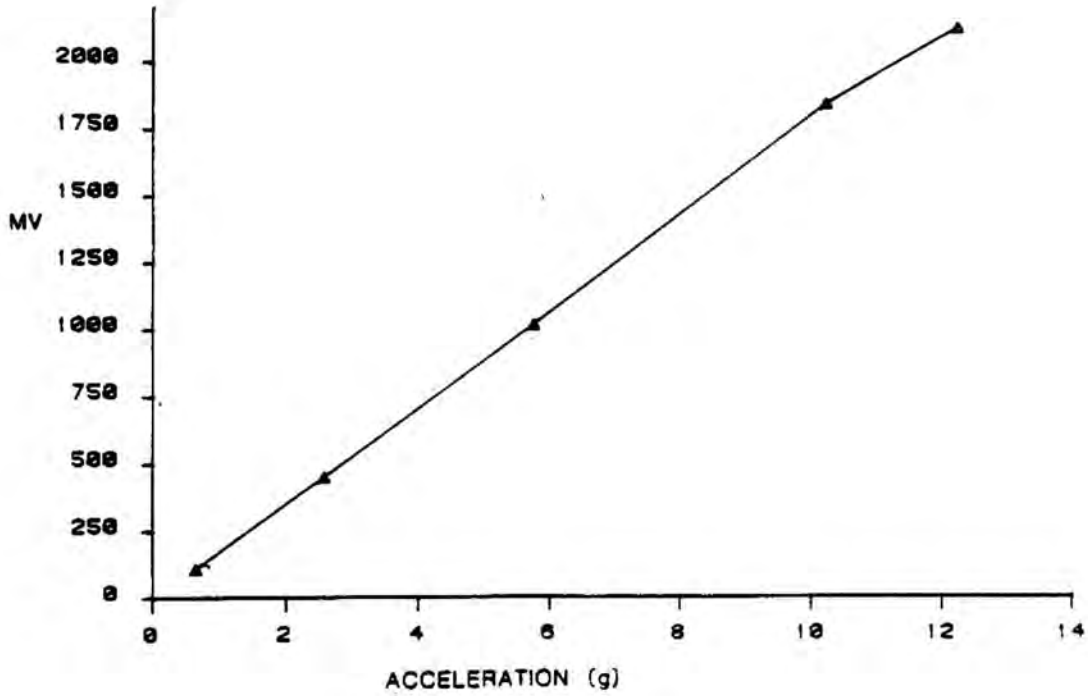
a = acceleration, inches $\cdot$ sec^{-2}

g = acceleration due to gravity, 386.09 in $\cdot$ sec^{-2}

f = frequency in Hz

mV = millivolts, RMS

Figure 4. Calibration of the accelerometer. An accelerometer was fastened to a plate attached to a motor with known frequencies and displacements. Acceleration was measured in mV at each frequency. Acceleration was calculated using the known frequencies and displacements. The regression relationship for acceleration vs mV was: $mV = 1.78\ g + 0$, $r = .9996$, $n = 5$ in one dog.


2000
1750
1500
MV
1250
1000
750
500
250
0
0
2
4
6
8
10
12
14
ACCELERATION (g)

where k is a constant, a is the acceleration and f is frequency. Due to this relationship tidal volume can be estimated during HFO by measuring acceleration at the chest wall.

Gases used in the experimental design

SF_6-O_2 and He-O_2

Two inspired gas mixtures were used. Both mixtures were composed of 20% O_2 with 80% helium (He-O_2) or sulfurhexaflouride (SF_6-O_2). Gas densities reported by Jaeger and Mathys (1968) are 0.45 and 4.20 $g \cdot L^{-1}$ for mixtures containing mainly He or SF_6, respectively. The gas density values were calculated using gas mixtures that also contained water vapor (6.7%) and CO_2 (3.2%). Gas mixtures were prepared gravimetrically and analyzed for gas content by Air Products and Chemicals Inc. (Tamaqua, PA) using gas chromatography. Gas tanks were mixed after delivery and oxygen content was checked before use by an infrared analyzer (Beckman LB-2 Medical Gas Analyzer, Beckman, Schiller Pk, PA).

Inspired gases were delivered through the small lumen (4 mm i.d.) of a cuffed HiLo Jet Tracheal Tube with an i.d. of 8 mm (Mallinckrodt; Argyle, NY) at the same flow rate for both gas mixtures. The flowmeter was calibrated separately for He-O_2 and SF_6-O_2 using a 120 L Respirometer (Collins, Braintree, MA).

SF_6-O_2-Halothane and He-O_2-Halothane

Two gas mixtures with different densities were used for the halothane uptake studies. Both gas mixtures contained 19.5% O_2, and 0.5% halothane, with 80% SF_6 (SF_6-O_2-Halothane) or helium (He-O_2-Halothane). Using a gravimetric method these gas mixtures were prepared in gas cylinders by Scott Medical Products (Plumsteadville,PA) and analyzed for halothane and oxygen

concentration using gas chromatography and infrared analysis. The tanks were mixed by rolling before use, both by the manufacturer and the experimental laboratory.

A theoretical calculation of the diffusion coefficients was made for SF_6-O_2-Halothane and He-O_2-Halothane, the mixtures used to deliver halothane during HFO. Binary diffusivities were calculated based on the Chapman-Enskog kinetic theory and the following equation presented by Bird et al., (1960):

$$D_{AB} = 1.858 \times 10^{-3} T^{3/2} \frac{[(MA+MB)/MAMB]^{\frac{1}{2}}}{P\sigma_{AB}^{2}\,\Omega_D} \qquad [9]$$

where D_{AB} = diffusion coefficient, $cm^2 \cdot s^{-1}$

T = temperature, K

M = molecular mass

P = pressure, atm

σ = characteristic length, Å

Ω_D = diffusion collision integral, dimensionless

D_{SF_6}, halothane = .0245752 $cm^2 \cdot s^{-1}$

D_{He}, halothane = .328004 $cm^2 \cdot s^{-1}$

D_{O_2}, halothane = .0705273 $cm^2 \cdot s^{-1}$

The characteristic length is a component of the Lennard-Jones potential for halothane which was not available from the literature and was thus calculated using procedures based on boiling points and Le Bas volumes (Reid et al, 1977). The calculated tertiary diffusivities for halothane in mixtures of either SF_6-O_2 or He-O_2 was estimated by the Wilke equation (Wilke, 1950):

$$\frac{1}{D'_{x,y}} = \left(\frac{1}{1-F_x}\right) \sum_{y=1}^{n} \frac{Fy}{D_{x,y}} \qquad [10]$$

x = halothane

y = one of the component gases in the mixture

F = fraction of the gases in question

$F_{SF_6} = .80$ $F_{He} = .80$

$F_{O_2} = .195$ $F_{O_2} = .195$

$F_{halothane} = .005$ $F_{halothane} = .005$ Halothane (0.5%)

diffusivity in either 80% SF_6-19.5% O_2 or 80% He-19.5% O_2 was calculated to be:

$$D' \text{ halothane, } SF_6, O_2 = 0.0281161 \text{ cm}^2 \cdot \text{s}^{-1}$$

$$D' \text{ halothane, He, } O_2 = 0.1886336 \text{ cm}^2 \cdot \text{s}^{-1}$$

The calculated diffusivity for halothane in a helium gas mixture was 6.7 times greater than that of the SF_6 gas mixture.

Sample collection and analysis

$PaCO_2$ and PaO_2

Arterial blood samples were obtained from indwelling catheters in all studies to monitor blood gas tensions and pH using the Corning Blood Gas Analyzer Model 165/2 (Corning, Medfield, MA). The PaO_2 measurement was performed by a Clark-type electrode. A Stow-Severinghaus type electrode measured PCO_2, and a flow through glass capillary and reference assembly measured pH. All blood samples were stored on ice and analyzed within ten minutes after each sample was taken. Blood samples were analyzed at 37 °C and the temperature of the animals was maintained using a heat lamp and warming blanket at 36-38 °C.

Arterial halothane

A technique similar to that described by Butler and Hill (1961) was used to extract halothane from the blood into n-heptane. Arterial blood was collected using one ml glass syringes and immediately immersed in 5 ml of

heptane using a 20 ga needle for transfer and then the samples were refrigerated until they were analyzed. Samples were analyzed by gas chromatography using a Hewlett Packard model 5710a gas chromatograph (Avondale, PA). The gas chromatography technique used to determine the halothane content in the blood was similar to that described by Rutledge et al., (1964),Kolmer et al., (1975) and Pang et al.,(1980). After further dilution with n-heptane, samples were injected into the chromatograph which was equipped with an electron capture detector and a .1% SP 1000 80/100 carbopac-C stainless steel column (10 ft x 1/8 in coiled). This column separates low weight hydrocarbons such as halothane primarily steriometrcally, that is by spatial arrangement of the molecules, and some by weight and polarization.

The electron capture detector consists of a radioactive isotope confined in a cell which ionizes by radiation the carrier gas flowing through the cell and a low voltage is applied to two electrodes. When halothane, an electron affinitive substance, enters the cell, it becomes a negative ion and then combines with positive ions causing a decrease in the ion current which is recorded as the chromatograph.

The halothane analysis conditions were as follows:

Carrier gas	-	Argon, 40 ml/min
Injection Port Temperature	-	150 °C
Column Temperature	-	200 °C
Detector Temperature	-	300 °C
Sample Injection	-	1-4 ul

To determine the validity of using the carbopac-C column to separate SF_6 and halothane in the samples, preliminary samples of n-heptane, halothane and n-heptane, and SF_6 halothane and heptane were injected into the gas

chromatograph. As shown in Appendix II the retention times for SF_6, halothane and heptane were separated sufficiently for qualitative measurement. A calibration curve for halothane was determined prior to the injection of the samples each day as shown in Appendix I. The unknown samples were within the range of calibration samples.

The efficiency of extraction of halothane by n-heptane from blood has been previously determined by Atallah and Geddes (1972) and Carvell and Stoward (1975) and found to be 97-98%. The extraction method was performed by placing a known weight of halothane into a known volume of blood, and, using a gas chromatograph with an electron capture detector the amount of halothane in the samples was measured and compared to the amount calculated based on the known weight of the halothane added to the blood samples.

Preliminary acceleration studies

In these experiments tidal volume was the volume estimated at the chest wall by the accelerometer. Tidal volume was dependent on gas density and the amount of stroke output. The stroke volume of the piston pump always remained the same. Stroke output was altered by using a lever to shunt part of the stroke volume of the piston pump away from the oscillatory delivery tube.

Acceleration was used to determine if both gas mixtures could be administered using the Emerson oscillator while tidal volume, as measured by an accelerometer, remained statistically unchanged. Either SF_6-O_2 or He-O_2 was administered to a training test lung (Vent Aid TTL, Grand Rapids, MI) and acceleration was measured during HFO at 30 Hz.

To measure acceleration and tidal volume independently, tidal volume was measured by body plethysomgraphy. A 10.9 kg dog premedicated with xylazine (0.5 mg/kg, s.c.) and glycopyrolate (0.02 mg/kg, s.c.) was anesthetized with pentobarbital (10 mg/kg) intravenously and placed in a plethysmograph (body

box) to measure tidal volume and an accelerometer was attached to the chest wall to measure acceleration. Volume and acceleration were measured at four HFO stroke outputs. Pressure changes reflected changes in tidal volume. Box pressure was measured by a Validyne MP 145 transducer (Validyne, Northbridge, CA). The body box was calibrated by injecting known volumes of air and the changes in pressure were recorded in millivolts. Values are presented in Table 2. The frequency response of the box was tested by measuring the pressure amplitudes during a frequency range of 12-34 Hz. At these frequencies the amplitude remained constant. A direct relationship between acceleration and volume displacement was established.

To test the relationship between acceleration, $PaCO_2$ and PaO_2, a 7.7 kg dog premedicated with xylazine (0.5 mg/kg, s.c.) and glycopyrolate (0.02 mg/kg, s.c.) was anesthetized with pentobarbital intravenously, intubated with a 7.0 mm i.d. triple lumen endotracheal tube and ventilated with HFO using a gas flow rate of 3 $L \cdot min^{-1}$. An accelerometer was fixed to the chest wall. A 20 gauge catheter was placed in a femoral artery to obtain blood samples for arterial blood gas analysis.

Using the HFO shunt valve, stroke output and tidal volume were changed and acceleration of the chest wall was measured. At each of the five stroke outputs blood gases were measured three, six, and nine minutes after the onset of HFO at 30 Hz. To assure a state of equilibrium, a nine minute measurement of $PaCO_2$ and PaO_2 was made and compared statistically using a paired t-test to the six minute sample. The analysis showed no difference between the six and nine minute means ± SE for $PaCO_2$ (34.1 ±1.3 mmHg, 34.2 ±1.4 mmHg) and PaO_2 (83.9 ±7.0 mmHg, 83.3 ±7.5 mmHg). All data shown are six minute samples. Data was recorded at five HFO stroke outputs.

Table 2. Calibration of Body Plethysmograph by Using Known Volumes and Measuring Voltage Changes (ΔmV)

$mV = .593\ ml + 0.014$ ($r = .98$, $n = 11$)

Volume (ml)	ΔmV
20	12.5
10	4.5
10	6.5
20	13.5
30	20.5
20	12.5
40	24.5
40	22.5
40	21.3
10	6.5
10	3.5

To study the effect of inspired gas density on volume delivered, acceleration was measured using a training test lung (Vent Aid TTL, Grand Rapids, MI) with SF_6-O_2 and He-O_2. Gas flow rate (3 $L \cdot min^{-1}$) and HFO frequency (30 Hz) were the same for both gas mixtures. Stroke output was adjusted using the shunt valve to change the tidal volume as measured by an accelerometer affixed to the bellows of the test lung.

$PaCO_2$ and PaO_2 vs Gas Density with HFO

Eight mongrel dogs 7.7-15 kg were premedicated with xylazine (0.5 mg/kg, s.c.) and glycopyrolate (0.02 mg/kg, s.c.). A catheter was inserted intravenously and an initial dose of pentobarbital (10 mg/kg) was administered. Anesthesia was maintained with subsequent doses of pentobarbital. Intubation was performed and the animal was ventilated with a volume ventilator (Harvard Apparatus Co., Millis, MA). Pancuronium (0.1 mg/kg) was administered to induce respiratory muscle paralysis. A 20 gauge catheter was inserted percutaneously into the femoral artery to obtain arterial blood samples for blood gas tensions and pH (Model 165/2; Corning, Medfield, MA).

SF_6-O_2 and He-O_2 were administered in varying order for each dog during a nine minute period with HFO. Frequency, acceleration, and gas flow were the same for both gas mixtures. Between each period of HFO ventilation the animals were ventilated for 20 minutes on positive pressure ventilation with room air. Arterial blood gas samples were taken at three, six, and nine minutes after the onset of HFO ventilation. The six and nine minute samples were analyzed using a paired t-test and there was no statistical difference between the means ±SE for PaCO2 (35.4 ±1.3 mmHg, 35.1 ±1.4 mmHg) and PaO_2 (80.0 ±8.0 mmHg, 82.1 ±7.9 mmHg). Therefore, the six minute samples are reported.

The effect of inspired halothane concentration on cardiac output (CO)

To determine if 0.5% halothane, the concentration used on the gas density studies, would decrease cardiac output significantly, six mongrel dogs 15-27 kg were anesthetized with pentobarbital (30 mg/kg), intubated with an 8.0 mm i.d. triple port endotracheal tube and ventilated with positive pressure ventilation. A catheter was inserted into a femoral artery to monitor blood pressure and obtain samples for blood gas analysis.

A Swan-Ganz Flow-Directed Thermodilution Catheter (Instrumentation Laboratories, Inc., Lexington, MA) was inserted into a femoral vein via a cut-down, advanced to the inferior vena cava, through the right heart chambers and into the pulmonary artery. The pressures at the catheter tip were monitored continuously and the final catheter placement was verified by the characteristic pressure wave form of the pulmonary artery. Cardiac output measurements were made using a thermodilution technique injecting 10 ml of room-temperature saline into the right atrium through the proximal lumen of the Swan-Ganz catheter and the cardiac output was calculated automatically using a Cardiac Output Computer Model 701 (Instrumentation Laboratories, Lexington, MA).

Inspired halothane was monitored with a Beckman LB-2 Halothane Gas Analyzer (Schiller Park, IL) which utilizes a non-dispersive infrared technique. Halothane exhibits a unique infrared absorption pattern, thus enabling the concentation of halothane in gas mixtures to be measured.

HFO was applied to each animal at 16, 25 and 34 Hz and a fresh gas flow of .5-.7% halothane with air was administered via a Fluotec Mark 2 vaporizer (Cyprane Ltd; Keighley, England) (10-15 L/min). For each frequency, fresh gas flow and inspired halothane were constant. Cardiac output was measured before the halothane was administered and 7 minutes after the onset of

halothane exposure. Cardiac output was measured at seven minutes because this was a time at which it was technically feasible. Cardiac output could not be measured at the same time blood samples were taken for blood gas or halothane analysis.

The effect of HFO frequency on the alveolar uptake of halothane

The objective of this study was to measure the effect of HFO frequency on the alveolar uptake of inspired halothane. Three of the above five adult mongrel dogs (16-25 kg) were ventilated with HFO at 16, 25 and 34 Hz. At each frequency halothane was administered at .5% for 10 minutes and analyzed with a Beckman infrared halothane analyzer. Arterial blood samples of one ml were obtained using one ml volume glass syringes at zero, one, two, three, four, five, ten, and 20 minutes after the onset of halothane administration to analyze for halothane content. At 20 minutes the halothane was discontinued and each dog was ventilated for 30 minutes with room air and positive pressure ventilation. The one ml blood samples were placed in a five ml volume of heptane in a glass vial and refrigerated until analyzed for halothane content.

The alveolar fraction of halothane (F_A) was assumed to equilibrate by diffusion with the arterial concentration of halothane and was expressed in mg%. The inspired concentration of halothane (F_I = 0.5%) was converted to mg% (mg per 100 ml blood) at 37 °C using the following equations:

$$mg\% = \frac{(MW_h)(F_I)(PC_h)}{(10)V_2} \qquad [11]$$

MW_h = Molecular weight Halothane = 197

F_I = inspired halothane concentration = .005

PC_h = Partition coefficient (halothane) = 2.3

(Papper and Kitz, 1963; Wylie and Churchill-Davidson, 1972; Eger, 1976)

V_2 = Volume (L), (310)(22.4)/ 273

[Charles Law $V_1/T_1 = V_2/T_2$]

[Ideal Gas Law = 197 g/ 22.4 L at STP (0 °C,760 mmHg)]

An inspired halothane concentration of 0.5% at equilibrium with the blood at 37 °C was calculated to be 8.907 mg%. Assumptions which have been made by others (Kety, 1951; Eger, 1976) with this calculation were 1) halothane behaves as an ideal gas; and 2) halothane is at blood tissue equilibrium within one second. Halothane concentrations were expressed as the ratio of the arterial concentration, which was assumed to equilibrate with the alveolar halothane concentration (F_A), to the concentration of the inspired halothane (F_I) (Eger, 1976).

The effect of gas density on the alveolar uptake of halothane

Five mongrel dogs,(7-11 kg), were premedicated with xylazine (0.5 mg/kg s.c.) and glycopyrolate (0.02 mg/kg s.c.). An intravenous catheter was inserted and pentobarbital 10 mg/kg was administered. Incremental doses (10-25 mg) of pentobarbital were given. After intubation the animal was ventilated with a positive pressure ventilator. Pancuronium (0.1 mg/kg) was given to induce respiratory muscle paralysis. A 20 gauge catheter was inserted percutaneously into a femoral artery to monitor blood pressure and obtain samples for blood gas tensions and halothane content. Rectal temperature was monitored and maintained at 36-38 °C with a hot water circulating pad and a heat lamp. An accelerometer was placed on the chest wall. Using the HFO shunt valve to change the stroke output of the HFO ventilator, effective tidal volume as measured by the accelerometer was made nearly constant for both gas mixtures.

A gas mixture of 80% SF_6-20% O_2 or 80% He-20% O_2 was given as the bias gas flow during HFO at 30 Hz for five minutes before the halothane gas

mixture was applied to attain a steady state. After five minutes measurements of blood pressure, arterial blood gas tensions, rectal temperature, and acceleration were made. Gas mixtures containing 80% SF_6 or 80% He, 0.5% halothane, 20% O_2, were administered for ten minutes in different orders at the same bias flow using a flowmeter which had been previously calibrated for both gas mixtures.

One ml volume blood samples were obtained in one ml glass syringes at zero, one-half, one, two, three, four, five, and 10 minutes for analysis of halothane content. After seven minutes of halothane exposure measurements of blood pressure, arterial blood gas tensions, pH, rectal temperature, and acceleration were taken. Halothane exposure ceased after ten minutes. The dogs were ventilated with a Harvard ventilator using room air for 30 minutes before re-exposure to halothane with a different carrier gas. The gas mixtures were given in varied order to each dog.

Statistical Analysis

Statistical analysis of data was carried out on a PDP 11/70 computer. The data for the blood gas tension studies were analyzed using a paired t-test. The physiologic parameter data measured during the halothane-gas density studies were analyzed using a three way ANOVA with repeated measures and the Wilcoxin Matched-Pairs Signed-Rank Test (Downie and Health, 1970). Linear regression analysis was used to test for a linear relationship between variables. In order to pool the halothane vs frequency data a two-way ANOVA was used to determine the effect of time and frequency. The halothane vs gas density studies were examined collectively and statistically by using the binomial distribution. The level of significance for all studies was chosen to be $p < 0.05$.

The halothane uptake data (F_A/F_I) were fit to a double exponential model using a modified non-linear least squares regression based on the Marquardt algorithm for parameter estimation as described by Horowitz and Homer (1970). The F_A/F_I for both gas mixtures were fit to a single uptake curve three parameter model which assumed the null hypothesis. The null hypothesis is that there is no difference in the F_A/F_I values for the two gas mixtures. The values were fit to a model of separate uptake curves for each gas mixture using six parameters. This model was the alternative to the null or the hypothesis. The two curves were the F_A/F_I values for SF_6-O_2 and He-O_2. To determine statistical difference between the null and the hypothesis the following equation with the F distribution was used:

$$F = \frac{SSE_{(null)} - SSE_{(hyp)}}{DF_{(null)} - DF_{(hyp)}} \Big\backslash \frac{SSE_{(hyp)}}{DF_{(hyp)}} \qquad [12]$$

where $SSE_{(null)}$ = sum of squares of the parameter estimates for the null

$SEE_{(hyp)}$ = sum of squares of the parameter estimates for the hypothesis

$DF_{(null)}$ = degress of freedom for the null

$DF_{(hyp)}$ = degrees of freedom for the hypothesis

RESULTS

Preliminary acceleration studies

To determine if acceleration could remain statistically unchanged with $He-O_2$ and SF_6-O_2 during HFO at 30 Hz, the gases were delivered to a training test lung. With the shunt closed the ventilator delivered the greatest oscillatory volume. For all shunt positions as shown in Figure 5 the acceleration for SF_6-O_2 was 56% of the acceleration for $He-O_2$. The rectangle in Figure 5 shows the shunt lever positions with the same acceleration for both gas mixtures. An acceleration of .19 g was obtained with the shunt closed using SF_6-O_2 and with the shunt 75% opened using $He-O_2$. These differences seen with changes in gas density are due to changes in airway impedence.

When using a dog rather than a training test lung, acceleration and tidal volume were measured independently. Tidal volume was measured using a body plethysmograph and found to be linearly proportional to acceleration when stroke output was changed and frequency held constant (Figure 6). There was a direct relationship between acceleration as measured by an accelerometer placed at the chest wall and volume displacement as measured by a body plethysmograph.

While ventilating a dog with HFO at 30 Hz, oscillatory stroke output was changed and changes in PaO_2, $PaCO_2$, and acceleration were measured. $PaCO_2$ decreased by 18% and PaO_2 increased by 19% for a 36% gain in acceleration (Figure 7). $PaCO_2$ is inversely related to gas exchange and tidal volume when frequency is held constant. Thus, the measurement of acceleration appears to estimate tidal volume during HFO.

Figure 5. Oscillatory stroke output vs. acceleration using the training test lung. Measurements are shown for $He-O_2$ and SF_6-O_2. Shunt closed indicates the maximum stroke output deliverd by the Emerson oscillator at 30 Hz. Shunt open indicates the minimum stroke output. An accelerometer was fixed to the bellows of the test lung at the same ventilator level position for both gas mixtures. $He-O_2$ and SF_6-O_2 were given at the same flow rate while the test lung was oscillated. At the same lever position the volume delivered to the bellows of the test lung as measured by accleration was less with SF_6-O_2 than with $He-O_2$. The box indicates the range of lever positions in which the tidal volumes as measured by acceleration were the same for both gas mixtures.

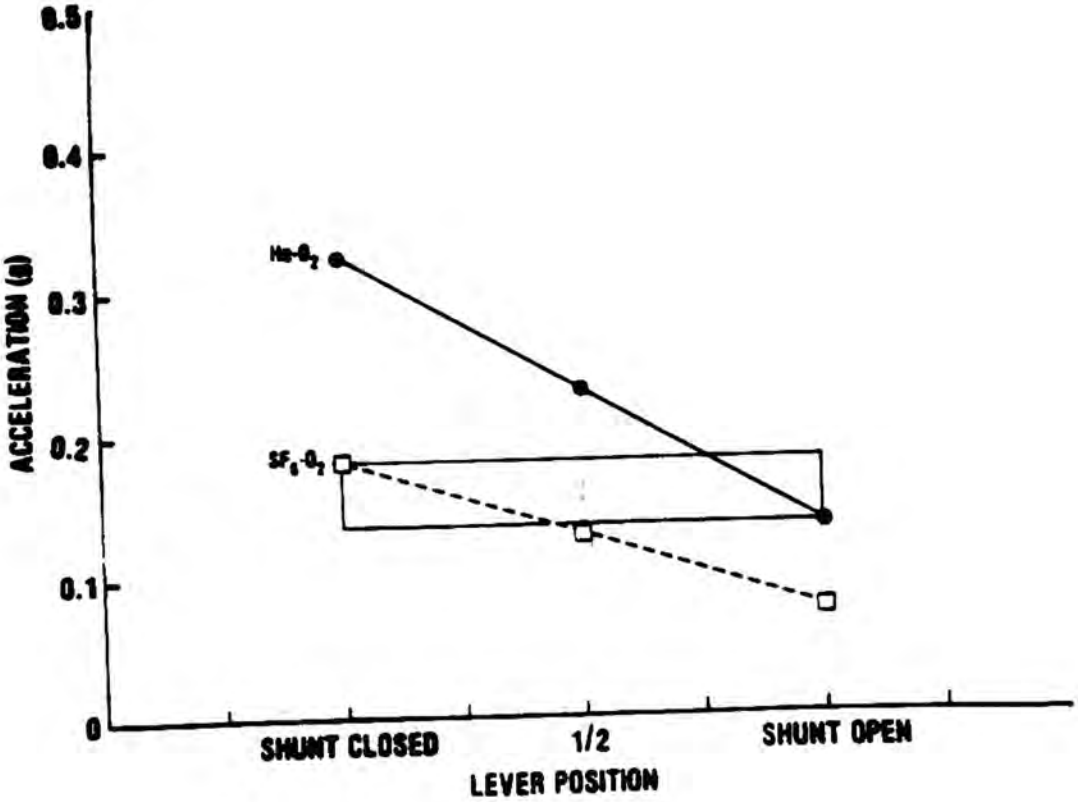

0.5
0.4
0.3
0.2
0.1
0
ACCELERATION (g)
He-O2
SF6-O2
SHUNT CLOSED
1/2
SHUNT OPEN
LEVER POSITION

Figure 6. Tidal volume vs. acceleration with variable oscillatory stroke output. While ventilating a 10.9 kg dog at 30 Hz, the output of the ventilator is varied by shunting portions of the stroke volume. Tidal volume was measured by plethysmograph while acceleration was measured at the chest wall. The following correlation between tidal volume and acceleration was measured:

$$V_t \text{ (ml)} = 86.82 \cdot a \text{ (g)} + 0.5 \text{ ml } (r = .98,\ n = 4)$$

where V_t is tidal volume measured in ml, a is acceleration measured in g, and $g = 9.8\ m \cdot sec^{-2}$.

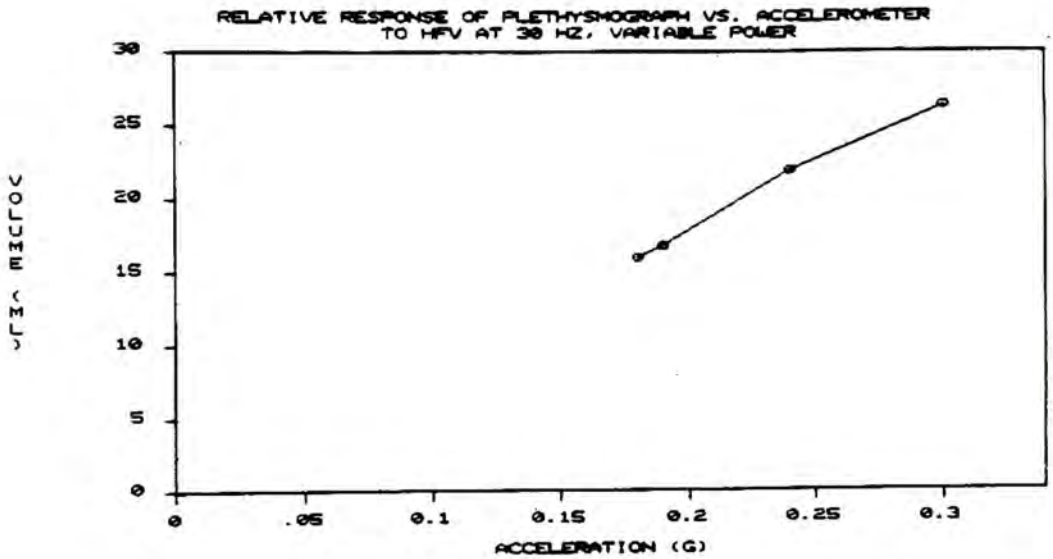
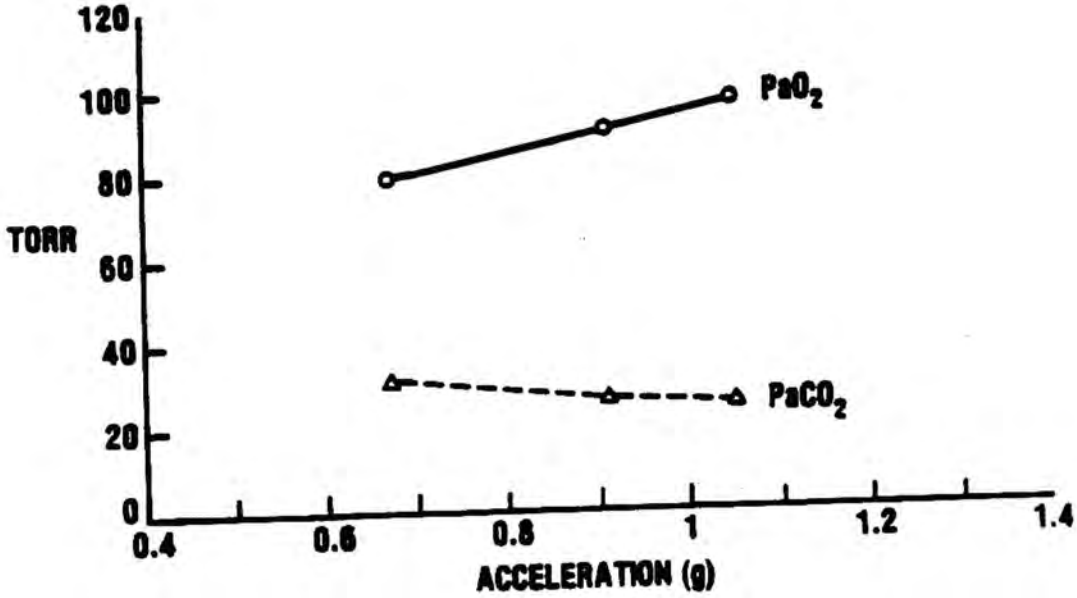

RELATIVE RESPONSE OF PLETHYSMOGRAPH VS. ACCELEROMETER
TO HFV AT 30 HZ, VARIABLE POWER
VOLTS
30
25
20
15
10
5
0
0
.05
0.1
0.15
0.2
0.25
0.3
ACCELERATION (G)

Figure 7. $PaCO_2$ and PaO_2 vs. Acceleration. While ventilating a dog at 30 Hz oscillatory stroke output was varied by shunting portions of the stroke volume. Arterial blood gases and acceleration were measured at three stroke outputs. $PaCO_2$ decreased from 31.1 to 25.4 mmHg and PaO_2 increased from 80.0 to 98.4 mmHg as accleration increased from 0.68 to 1.08 g.


120
100
80
60
40
20
0
TORR
PaO2
PaCO2
0.4
0.6
0.8
1
1.2
1.4
ACCELERATION (g)

$PaCO_2$ and PaO_2 vs gas density with HFO

The mean values ± SE for $PaCO_2$ and PaO_2 using HFO with different density gases are presented in Table 3 and Figure 8. Acceleration change was prevented when gas mixtures were changed by adjusting the shunt valve. $PaCO_2$ decreased significantly in the presence of SF_6-O_2 (He-O_2 = 38.1 ± 2.7 mmHg vs. SF_6-O_2 = 30.6 ± 2.0 mmHg) and PaO_2 increased significantly in the presence of SF_6-O_2 (He-O_2 = 70.3 ± 6.2 mmHg vs. SF_6-O_2 = 89.8 ± 6.4 mmHg) indicating a density dependence of gas transport with HFO not present with conventional ventilation (Worth et al., 1976). During HFO gas exchange as measured by $PaCO_2$ and PaO_2 improved with increased density of the inspired gas.

The effect of inspired halothane on cardiac output (CO)

Cardiac output was measured in six anesthetized dogs ventilated with HFO at frequencies of 16, 25, and 34 Hz with .5% halothane. No significant difference in cardiac output was measured between zero and 7 minutes after the onset of halothane administration for 16 HZ (2.6 ± 0.4, 2.8 ± 0.6 $L \cdot min^{-1}$), 25 Hz (2.2 ± 0.2, 2.1 ± 0.2 $L \cdot min^{-1}$), and 34 Hz (2.3 ± 0.4, 2.3 ± 0.4 $L \cdot min^{-1}$) (Figure 9). Thus, there was no evident effect on cardiac output with small concentrations of inspired halothane during HFO.

The effect of halothane and gas density on physiologic parameters

Figure 10 shows the effect of .5% halothane and gas density on $PaCO_2$, PaO_2, blood pressure, acceleration, temperature, and pH during HFO. $PaCO_2$ significantly decreased with the SF_6-O_2 gas mixture as compared with the He-O_2 gas mixture, and PaO_2 increased with SF_6-O_2 at the seven minute measurement as analyzed by the Wilcoxin rank sign test ($p < 0.05$). Concomittantly, pH decreased significantly with the SF_6-O_2 gas mixture. There were no significant differences in temperature or acceleration with either gas mixture. Acceleration was matched for both gas mixtures with a conservative bias,

Table 3. Changes in $PaCO_2$ and PaO_2 in eight dogs using HFO at 30 Hz with gases of different density

	$He-O_2$		SF_6-O_2		% Difference in Acceleration
Dog #	$PaCO_2$ (mmHg)	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	PaO_2 (mmHg)	$(He-SF_6)/He$ (%Δ)
1	50.0	48.0	40	58.9	+ 21
2	38.9	63.9	26.5	110.0	- 06
3	46.5	56.6	26.0	66.0	- 01
4	38.4	68.0	36.8	96.1	+ 10
5	37.0	79.4	27.7	88.4	+ 21
6	25.9	58.3	23.3	105.6	0
7	32.0	97.3	32.7	95.2	0
8	36.4	91.2	31.5	98.0	+ 07
Mean ± SE	38.1 ± 2.7	70.3 ± 6.2	30.6 ± 2.0*	89.8 ± 6.4*	+ 06.6 ± 3.6

* Significantly different from $He-O_2$ ($p < 0.05$).

Values are means ± SE.

$He-O_2$ = 80% He, 20% O_2.

SF_6-O_2 = 80% SF_6, 20% O_2.

$PaCO_2$ and PaO_2 = arterial blood gases at six minutes after the onset of HFO.

n = 8.

Figure 8. $PaCO_2$ and PaO_2 for $He-O_2$ and SF_6-O_2 during HFO ventilation at 30 Hz with matched acceleration and flow rate for gas mixtures. Values are mean ± SE, n = 8. $PaCO_2$ = arterial $PaCO_2$ (mmHg) after six minutes of ventilation with a gas mixture. PaO_2 = arterial PaO_2 (mmHg) after six minutes of ventilation with a gas mixture. He = .80 Helium, .20 O_2. SF_6 = 0.80 SF_6, .20 O_2.

*Significant difference of SF_6-O_2 compared with $He-O_2$ ($p < 0.05$).

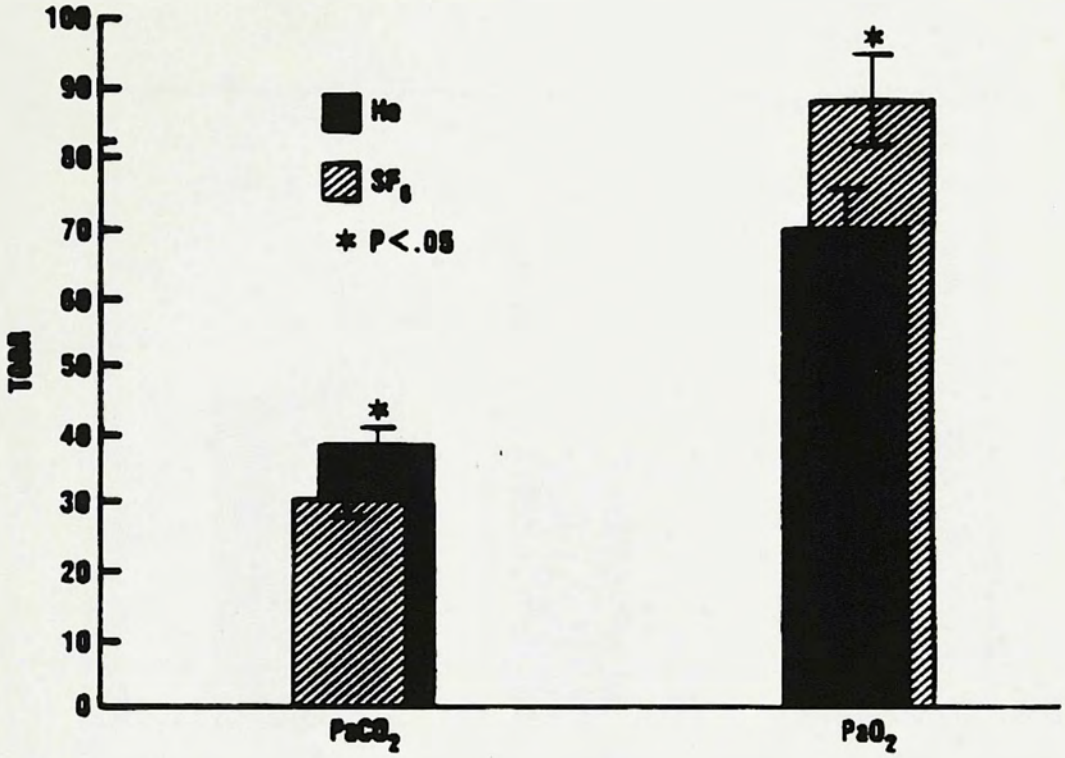

100
90
80
70
60
50
40
30
20
10
0
He
SF6
* P<.05
*
*
PaCO2
PaO2

Figure 9. The change in cardiac output (CO) during HFO at frequencies of 16, 25, and 34 Hz in 6 dogs before and during the administration .5-.7% halothane for seven minutes. Values are mean ± SE. L/min = liters per minute.

0 = no halothane

7 = seven minutes after the onset of .5-.7% halothane

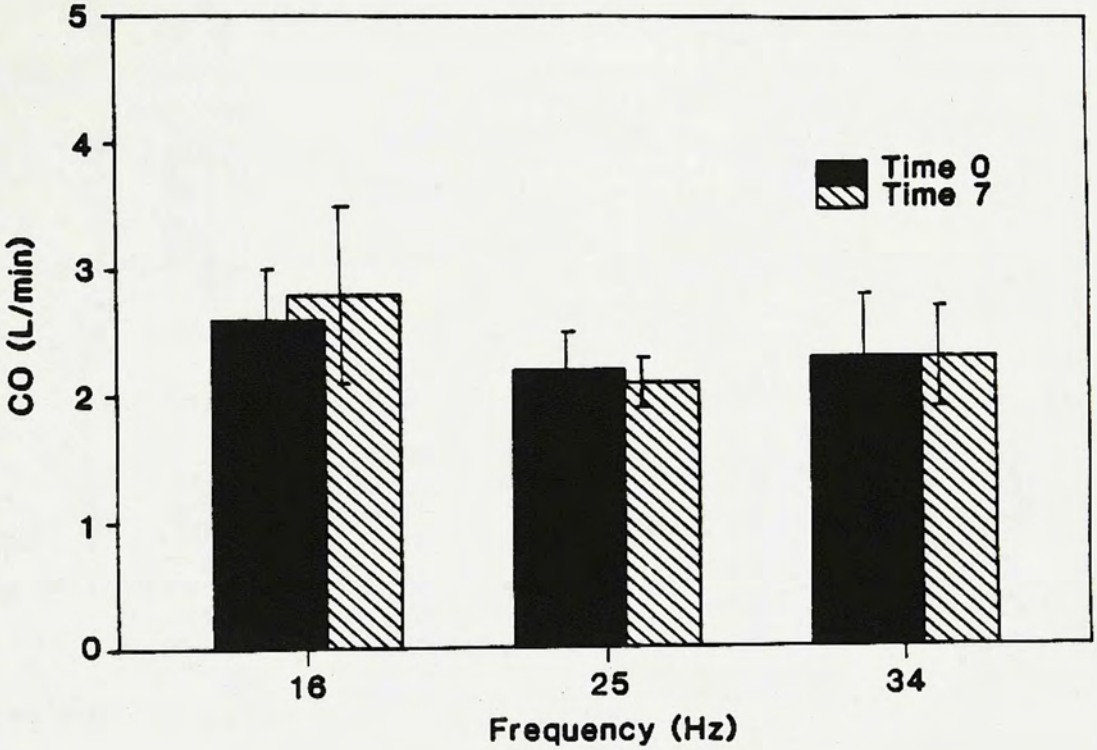

5
4
3
2
1
0
CO (L/min)
Time 0
Time 7
16
25
34
Frequency (Hz)

Figure 10. Initial (0 minutes) and final (7 minutes) values of physiological parameters in the two gas mixtures during HFO at 30 Hz with 0.5% halothane in the two gas mixtures.

Values are mean ± SE.

$PaCO_2$ = arterial CO_2 (mmHg)

PaO_2 = arterial O_2 (mmHg)

BP = mean arterial blood pressure (mmHg).

TEMP. = temperature (°C).

ACCEL. = acceleration (g)

SF_6-O_2 = 80% SF_6 - 19.5% O_2 - .5% halothane.

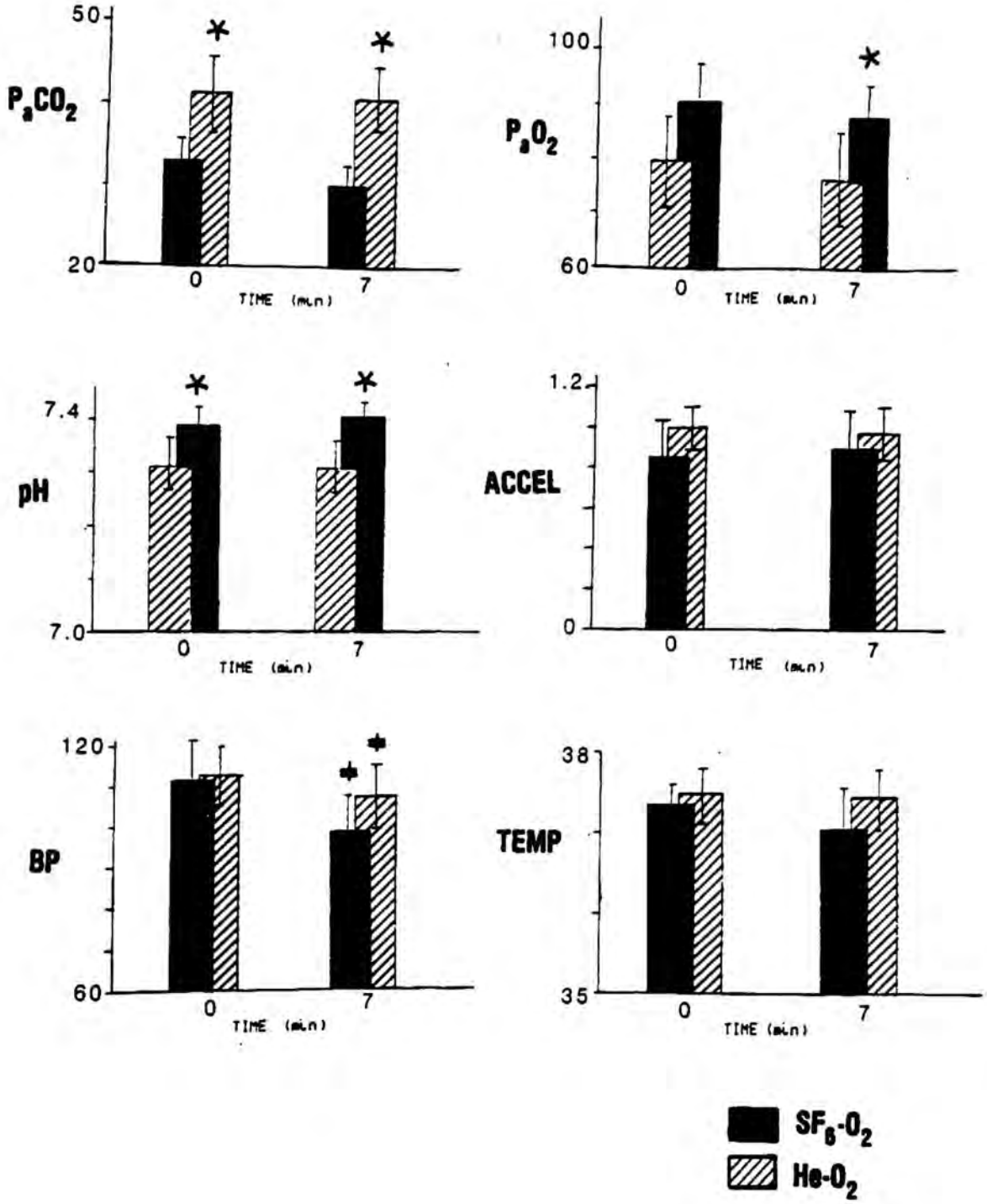
He-O_2 = 80% He - 19.5% O_2 - .5% halothane.

0 minutes = no halothane.

7 minutes = 7 minutes after the onset of .5% halothane.

*Significant difference between 0 and 7 minute values ($P < 0.05$) for both gas mixtures.

+ Significant difference between He-O_2 and SF_6-O_2 values ($p < 0.05$).


50
20
P_aCO_2
0
7
TIME (min)
100
60
P_aO_2
0
7
TIME (min)
7.4
7.0
pH
0
7
TIME (min)
1.2
0
ACCEL
0
7
TIME (min)
120
60
BP
0
7
TIME (min)
38
35
TEMP
0
7
TIME (min)
SF_6-O_2
He-O_2

i.e., the mean value for acceleration was greater with He-O_2 than with SF_6-O_2. Blood pressure decreased over time indicating a depressor effect of halothane with both gas mixtures.

The effect of HFO frequency on the alveolar uptake of halothane

Halothane can be used as a tool to measure gas transport during HFO because with an increase in ventilation there is an increase in alveolar concentration of halothane with conventional ventilation (Kety, 1951; Papper and Kitz, 1963). Our halothane uptake studies were similar to our blood gas studies with the exception that arterial blood halothane concentrations rather than $PaCO_2$ and PaO_2 were measured with gas density changes. The arterial blood halothane concentrations are expressed as the F_A/F_I ratio. The arterial concentration of halothane (Fa) is expressed in mgm%. F_A, the alveolar concentration of halothane, cannot be measured with HFO. According to Eger (1976), Fa is equal to F_A. The inspired concentration of halothane (F_I) is expressed in % of the inspired gas. Identical units must be used to calculate a ratio, thus, F_I must be converted to mgm%.

Halothane was administered in one set of studies at frequencies of 16, 25, and 34 Hz to determine whether it could be administered with HFO and if halothane could be used as a marker to identify changes in ventilation and gas transport with HFO. Figure 11 shows the effect of HFO frequency on the rate of alveolar uptake of halothane (.5%) in one dog. Table 4 shows equation [13] which was fit with the alveolar halothane (F_A/F_I) data. This exponential equation is similar to the double exponential model described by Kety (1951) which gives an estimate of F_A/F_I based on the solubility of a gas in the blood, the alveolar minute ventilation, and the cardiac output using four

Figure 11. The alveolar uptake of .5% halothane (F_A/F_I) vs. time after the onset of halothane as a function of HFO frequency (16, 25 and 34 Hz) in one dog. Arterial halothane was measured over time after the onset of halothane administration and expressed as the F_A/F_I ratio. The equation shown was fit to the F_A/F_I data for the three frequencies.

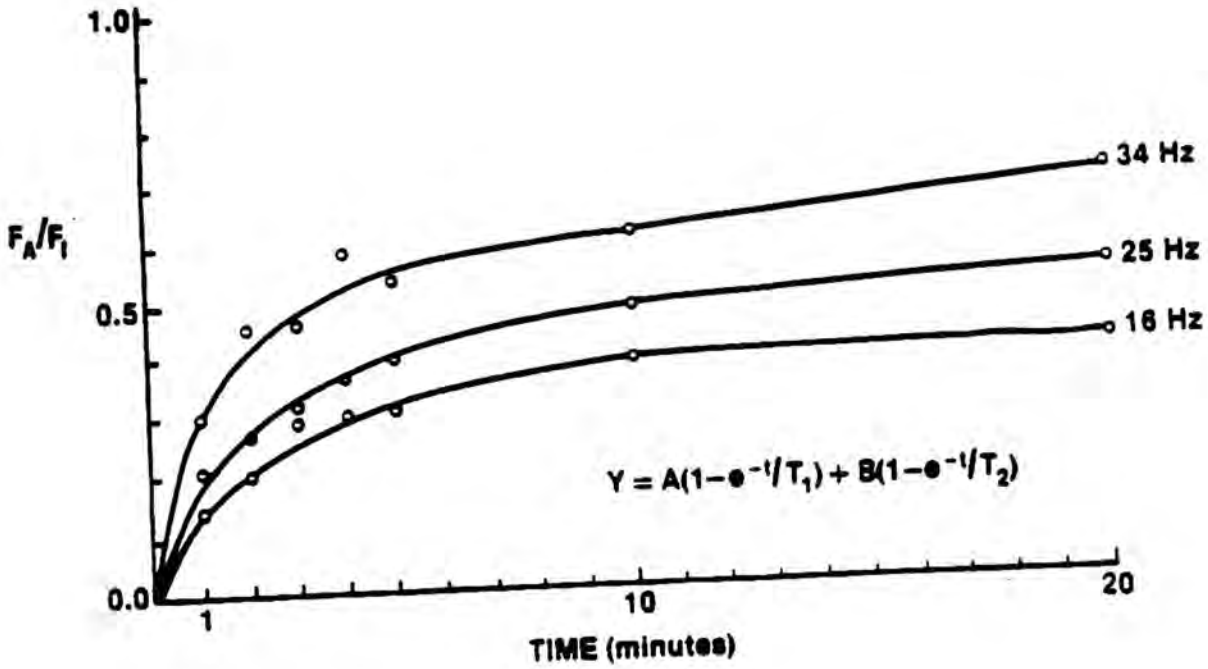

1.0
0.5
0.0
F_A/F_I
34 Hz
25 Hz
16 Hz
$Y = A(1-e^{-t/T_1}) + B(1-e^{-t/T_2})$
1
10
20
TIME (minutes)

Table 4. Parameters for the alveolar uptake of halothane during HFO at different frequencies using the data from Figure 11 for one dog.

$$F_A/F_I = A[1-e^{-t/T(1)}] + B[1-e^{-t/T(2)}] \qquad [13]$$

	Parameters			
	A	B	T(1)	T(2)
16 Hz	0.304	0.091	0.267	5.31
25 Hz	0.399	0.154	0.170	3.72
34 Hz	0.641	0.485	0.022	1.02
r =	.97	.93	.99	.99

A = asymptote for the fast component

B = asymptote for the slow component

T(1) = time constant for the fast component, minutes

T(2) = time constant for the slow component, minutes

F_A/F_I = alveolar halothane concentration/inspired halothane concentration

r = regression coefficient for frequency vs A, B, T(1), and T(2)

independent parameters consisting of two asymptotes and two time constants. The parameters of equation [13] in Table 4 are A and B, the asymptotes for the fast and slow component of the double exponential equation, and T(1) and T(2), the time constants for the fast and slow component of the double exponential equation. The equation was fit to the F_A/F_I data for the three frequencies and the best estimates for the parameters are listed in Table 4. There was a direct correlation of frequency and the four parameters of the model as shown in Table 4 indicating that as ventilation increases with an increase in frequency, the two asymptotes increase and the two time constants decrease. With an increase in the value of the asymptotes there is an increase in the final F_A/F_I value indicating an increase in halothane uptake. A time constant is defined as the amount of time necessary for a substance to reach 63.2% of its asymptote. If a time constant decreases, then by definition, the alveolar uptake of halothane (F_A/F_I) for any given time has increased. In three dogs F_A/F_I increased progressively ($p < 0.05$) with increasing frequency at each time studied (Figure 12). According to Eger (1976) with an increase in ventilation there is a more rapid rise in alveolar halothane (F_A/F_I). That is, the greater the ventilation the more rapid the approach of the alveolar to the inspired concentration. Thus, as HFO frequency increased, gas transport increased as measured by the rate of alveolar uptake of halothane. These data indicate that halothane can be administered with HFO and differences in ventilation may be indicated using alveolar uptake of halothane as an indicator.

The effect of gas density on the alveolar uptake of halothane

Table 5 lists the B(1) and B(2) parameters and the double exponential equation [14] used for the halothane vs gas density studies. The statistical analysis used was similar to that described by Peck and Barrett (1979). To

Figure 12. The effect of HFO frequency on the alveolar uptake of halothane in 3 dogs. Values are mean ± SE. The lines indicate different times after the onset of halothane administration (1, 5, and 10 minutes). A significant difference was found between each of the times and each of the frequencies as analyzed by a two-way ANOVA ($p < 0.05$).

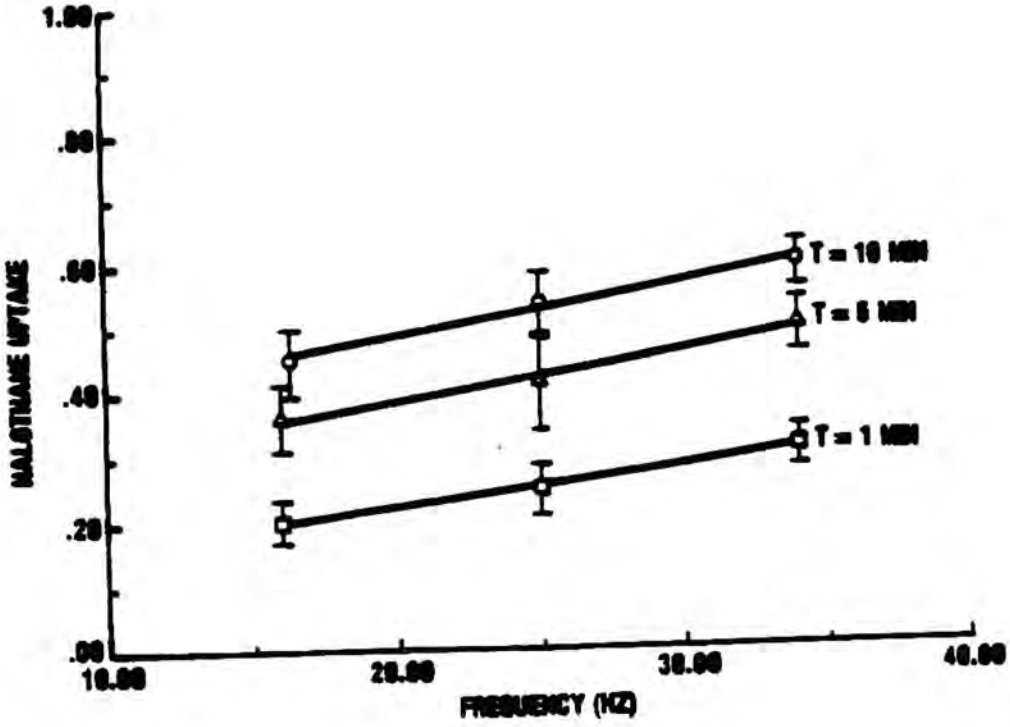

1.00
.80
.60
.40
.20
.00
HALOTHANE UPTAKE
T = 10 MIN
T = 5 MIN
T = 1 MIN
10.00
20.00
30.00
40.00
FREQUENCY (HZ)

Table 5. Parameters for the exponential model fit for the alveolar uptake of halothane with inspired gases of different density.

$$F_A/F_I = B(1)[1-e^{-B(2)t}] + (1-B(1))[1-e^{-.01B(2)t}] + B(3) \qquad [14]$$

Dog	Parameter: Gas:	B(1) He	B(1) SF6	B(2) [minutes^{-1}] He	B(2) [minutes^{-1}] SF6	F*
1		.14 ± .02	.54 ± .05	5.60 ± .81	.36 ± .81	27.11
2		.32 ± .05	.52 ± .09	1.68 ± 1.02	1.88 ± 1.23	4.12
3		.44 ± .04	.68 ± .05	.61 ± .14	.40 ± .16	21.45
4		.16 ± .03	.23 ± .03	6.05 ± .58	6.81 ± .85	4.85
5		.23 ± .03	.21 ± .03	1.99 ± .51	3.55 ± .76	1.73

* For $p < 0.05$, $F(3,10)$ 3.71; p 0.01, $F(3,10)$ 6.55

Parameter values are reported with 1 SE.

B(1) = asymptote for the fast component

B(2) = time constant for the fast component

B(3) = offset for data collected after one series of halothane administration

F_A/F_I = alveolar halothane concentration/inspired halothane concentration

He = 80% helium, .5% halothane, 20% O_2.

SF_6 = 80% SF_6, .5% halothane, 20% O_2.

improve the mathematical estimation of the curve from the data the equation from Figure 11 was changed. A decrease in the number of parameters from 4 to 2 increased the degrees of freedom which indicated an improvement in the fit of the equation to the data. Thus, a relationship between the two time constants and two asymptotes was estimated. B(1) is the asymptote and B(2) is the time constant for the fast component of the double exponential equation. Two assumptions were made with this equation. The first assumption was that the final asymptote was equal to one. Thus, B(1) and 1-B(1) are the two asymptote values. That is, that the final alveolar concentration of halothane is equal to the inspired concentration of halothane. The second assumption was that the second time constant was 100 times the first time constant. This was the best ratio for the two time constants out of the three ratios tested (1:50, 1:100 and 1;200). The three ratios for the time constants were tested by fitting each of the three equations to the same data and choosing the anaysis with the lowest sum of squares as the best equation for the data.

The second group of data for each experiment, either He-O_2 or SF_6-O_2, contained halothane at time zero because not all of the halothane was eliminated from the lungs after the first administration of halothane. For this reason the B(3) parameter was added to allow the curve to begin at a positive number at zero time. For the largest B(3) value which is 0.1, this introduced a 10% error when time is equal to infinity because F_A/F_I will be equal to 1.1. Time of infinity, or the time at which F_A/F_I is equal to one, is approximately 7 hours, a time much greater than ten minutes which is the period of time over which the data was collected. Using the standard errors of the parameters for this particular group of data, it was determined that there was a ±20% error at seven hours. Thus, this addition of the B(3) parameter does not appear to introduce a significant error. Additionally, when the

equations with and without the B(3) parameter were compared it was determined that the equation with the B(3) parameter did statistically improve the equation to fit the data.

An analysis of variance was performed on the five groups of data and determined that the addition of three parameters to describe the uptake of halothane in the second gas mixture was statistically justified by improvement in the fit of the data in four of the animals. The standard errors of the estimated parameters of the time constants for the SF_6-O_2 and He-O_2 gas mixtures were large compared to the parameters. The model presumably could not make a precise estimate of the time constants because the apparent time constants extended beyond the range of the data; i.e., less than .5 minutes and greater than ten minutes for the fast and slow time constants, respectively.

Figure 13 illustrates the difference between the rate of alveolar uptake for halothane (F_A/F_I) with the two gas mixtures, SF_6-O_2 and He-O2, for one dog ventilated with HFO at 30 Hz. With SF6-O2 a more rapid rise in alveolar uptake of halothane (F_A/F_I) was seen. The double exponential equation described above was fit to the F_A/F_I data for both gas mixtures. By analysis of variance it was found that two individual curves fit the data better than one. This analysis shows at any particular time from zero to ten minutes after the onset of inspired halothane with HFO at 30 Hz the concentration of halothane in the arterial blood is greater with SF_6-O_2 than it is with He-O_2. These results indicate that gas transport as measured by the alveolar uptake of halothane with HFO appears to be more efficient in the presence of the inspired gas SF_6-O_2 in four out of the five experiments in which it was measured.

Figure 13. Halothane uptake expressed as (F_A/F_I) in one dog during HFO at 30 Hz with SF_6-O_2 vs. He-O_2. The F_A/F_I values were fit to the double exponential model using the Marquart least squares analysis to obtain the best fit. By analysis of variance the two uptake curves were significantly different ($p < 0.05$).

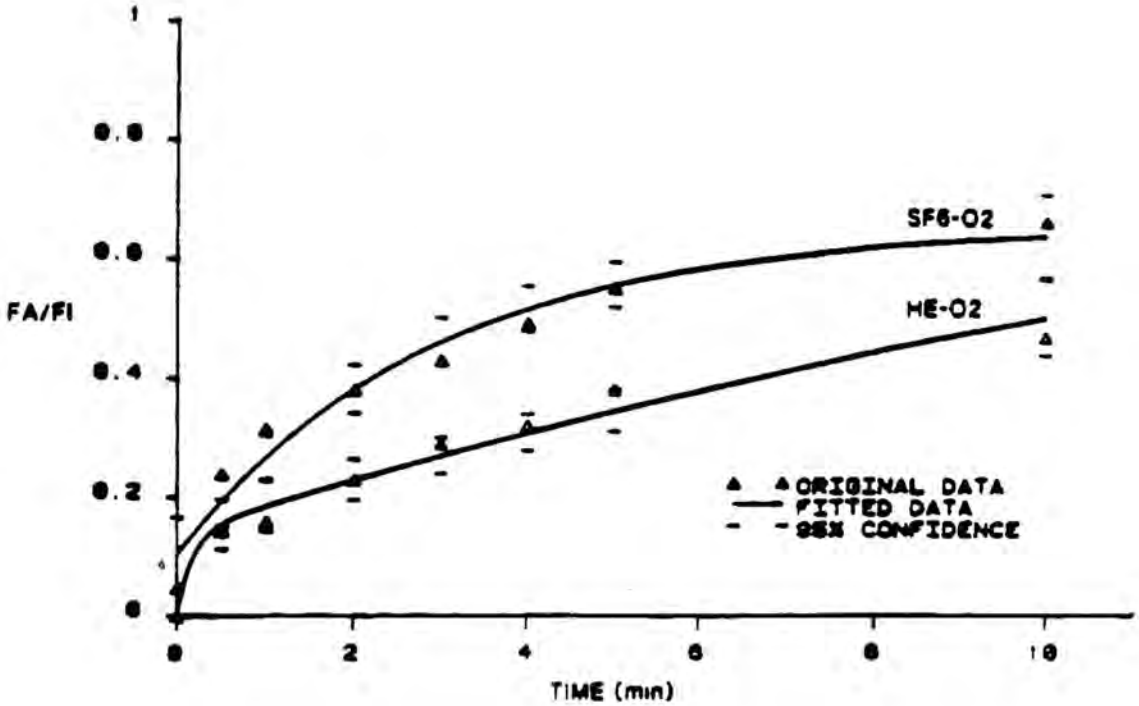

1
0.8
0.6
0.4
0.2
0
FA/FI
SF6-O2
HE-O2
ORIGINAL DATA
FITTED DATA
95% CONFIDENCE
0
2
4
6
8
10
TIME (min)

Figure 14 shows the F_A/F_I values and curves which fit the data using the double exponential equation described in Table 5 for five dogs. Using an F test, the first four sets of data show that halothane concentration in the arterial blood in the presence of SF_6-O_2 was significantly greater when compared with He-O_2 at any particular time from one to ten minutes. The last set of data revealed no significant difference between the rate of alveolar uptake of halothane for the two gas mixtures.

The F_A/F_I values for the five experiments are shown in Figure 15. The diagonal line is the line of identity indicating the same rate of gas transport of halothane for both gas mixtures. To the left of the diagonal line are the data when halothane was transported into the blood faster during the SF_6-O_2 gas mixture than the He-O_2 gas mixture. The line connecting the data points is from one experiment and appears furthest away from the diagonal line indicating the largest difference in the rate of transport of halothane between the two gas mixtures. An analysis using a binomial distribution demonstrated that alveolar uptake of halothane is greater in the presence of SF_6-O_2 ($p < 0.001$).

Correlation of differences in $PaCO_2$ and differences in the F_A/F_I values

Eger (1976) has shown with conventional ventilation that the uptake of halothane is dependent on ventilation. The relationship between ventilation and $PaCO_2$ is given in the following equation:

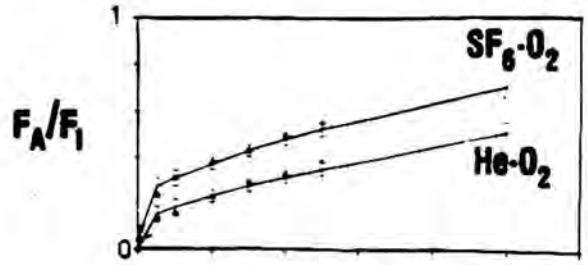
$$PaCO_2 = \dot{V}CO_2 / \dot{V}_A \cdot K$$

where $\dot{V}CO_2$ is the CO_2 production, $\dot{V}_A$ is the effective alveolar ventilation and K is a constant (West, 1981). If ventilation is doubled $PaCO_2$ is halved.

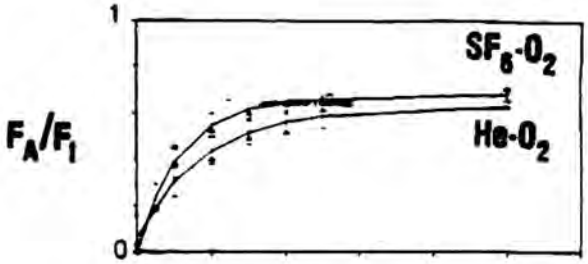
Figure 14. The change in the alveolar uptake of halothane when inspired gas density was changed in five dogs during HFO at 30 Hz with constant acceleration. Halothane uptake (F_A/F_I) was significantly different for four out of five experiments when gas density was changed (Table 5). The fifth experiment showed no difference between the two gas mixtures.

$$\Delta\ PaCO_2 = PaCO_2(He\text{-}O_2) - PaCO_2(SF_6\text{-}O_2)$$

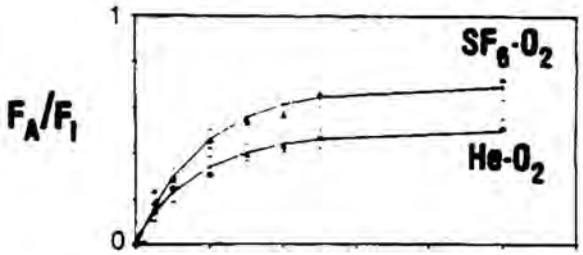
The difference in $PaCO_2$ between gas mixtures was greatest for the experiments with the greatest difference in halothane uptake.



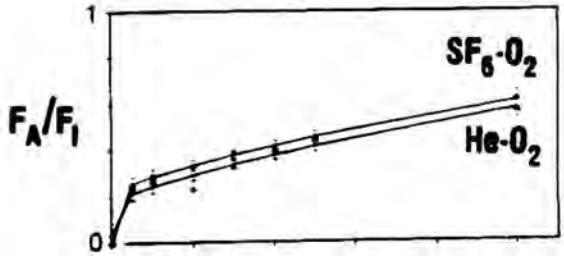
$\Delta P_aCO_2 = 10.9$ mmHg



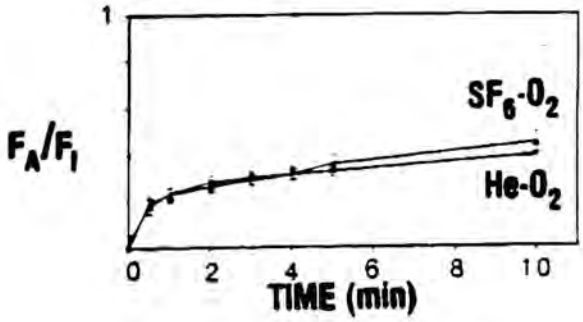
$\Delta P_aCO_2 = 4.1$ mmHg



$\Delta P_aCO_2 = 12.3$ mmHg

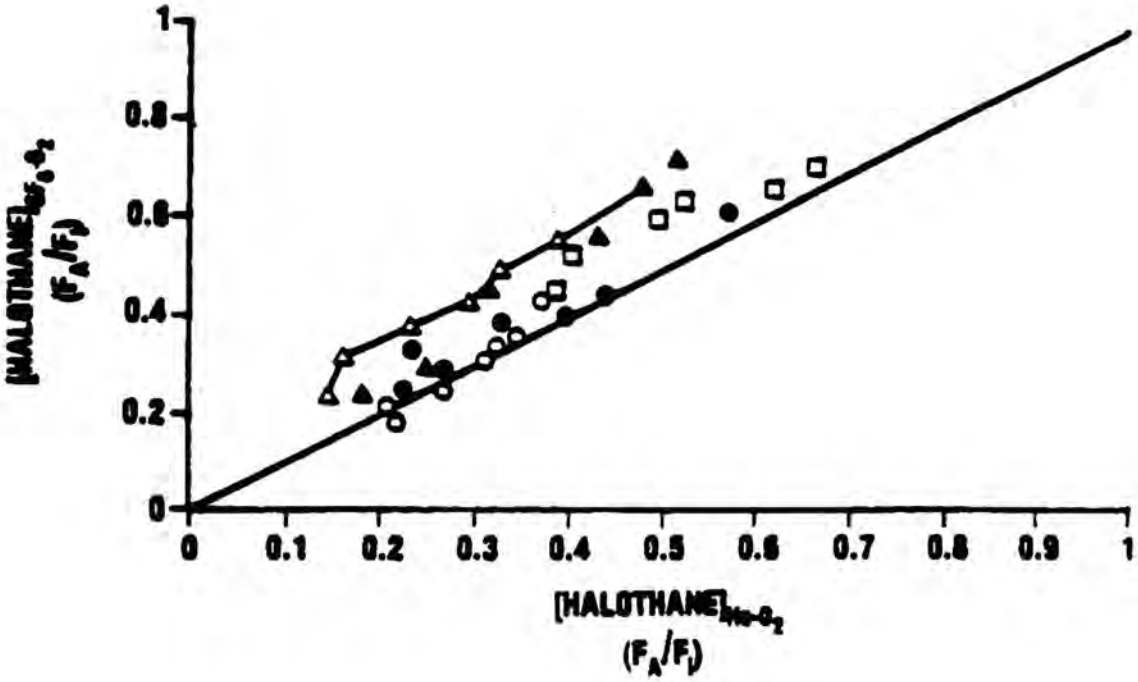


$\Delta P_aCO_2 = 7.3$ mmHg



$\Delta P_aCO_2 = 4.1$ mmHg

Figure 15. Values for F_A/F_I for He-O_2 vs. SF_6-O_2. The abscissa for each value is F_A/F_I with He-O_2. The ordinate is F_A/F_I in the same dog at the same elapsed time after the onset of halothane administration with SF_6-O_2. The diagonal line represents unity. Points falling on this line show no difference in the F_A/F_I ratios between the gas mixtures. Values to the left of the diagonal line indicate the greater rate of transport of halothane with SF_6-O_2 than with He-O_2. The distance of the points from the line of equality was proportional to the difference in the rate of uptake of halothane with the two gas mixtures. The rate of uptake of halothane was significantly greater with SF_6-O_2 compared with He-O_2 ($p < 0.001$).


1
0.8
0.6
0.4
0.2
0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
[HALOTHANE]
(F_A/F_I)
[HALOTHANE]
(F_A/F_I)

To account for a portion of the variability between experiments the relationship of the differences in $PaCO_2$ of the two gas mixtures and the differences in the B(1) parameter listed in Table 5 and F_A/F_I for each experiment were examined (Figure 16). As the difference in the $PaCO_2$ increased, the difference in B(1) increased. This was also seen in the relationship between the difference in $PaCO_2$ and the difference in F_A/F_I (Figure 17). This correlation shows a direct relationship between ventilation as measured by $PaCO_2$ and the rate of rise of the F_A/F_I ratio.

Figure 16. The differences in $PaCO_2$ vs. B(1) parameter for SF_6-O_2 vs. He-O_2. The line represents the linear regression for the differences in B(1) and $PaCO_2$ for the five experiments.

$$p < 0.05, \ (F = 10.38,, \ \Delta B(1) = .012356 \cdot \Delta PaCO_2).$$

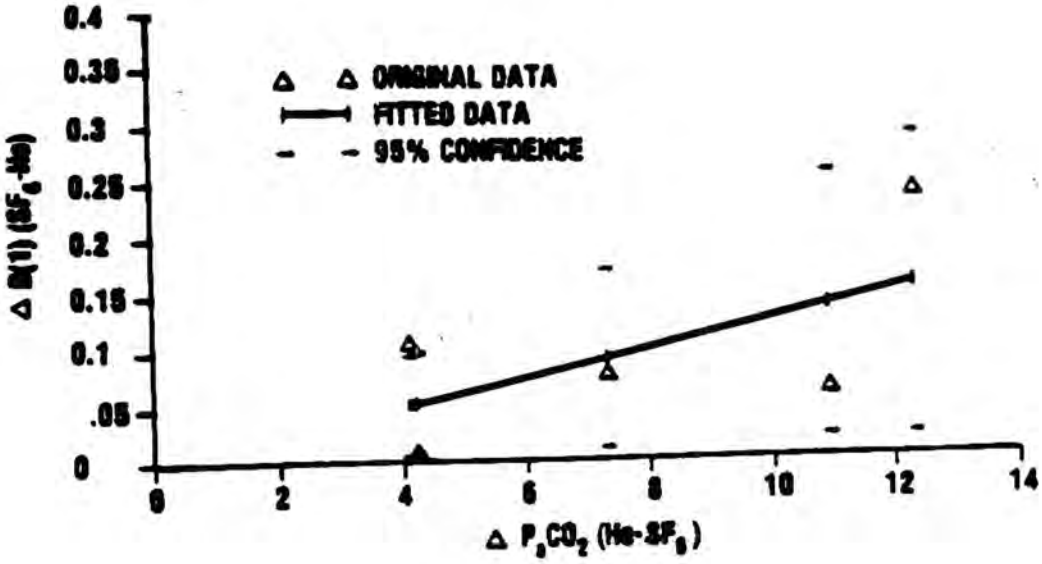
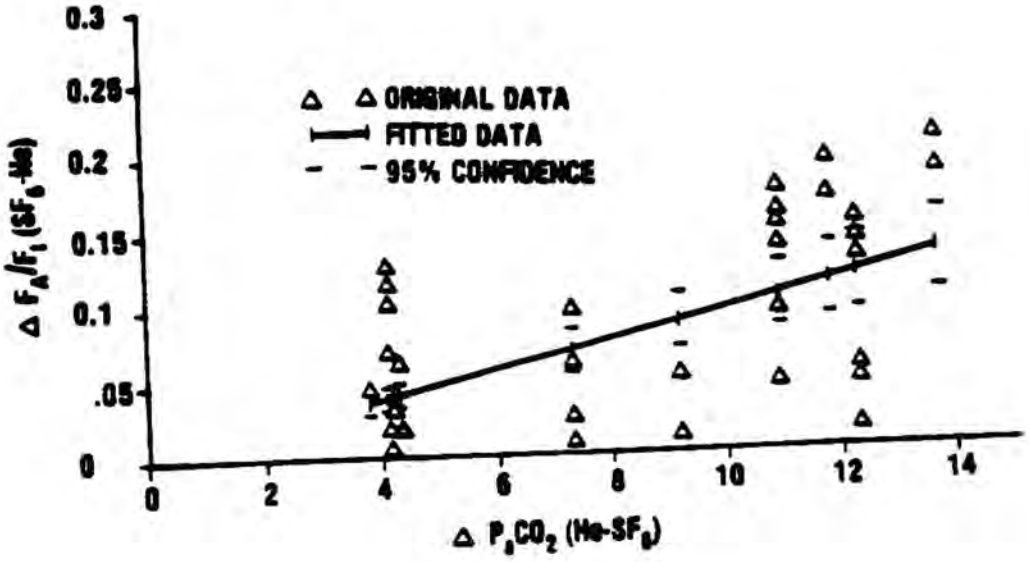

0.4
0.35
0.3
0.25
0.2
0.15
0.1
.05
0
0
2
4
6
8
10
12
14
Δ ORIGINAL DATA
FITTED DATA
95% CONFIDENCE
Δ P$_s$CO$_2$ (He-SF$_6$)

Figure 17. The differences in $PaCO_2$ vs. the differences in F_A/F_I for SF_6-O_2 and He-O_2. The line represents the linear regression for the differences in F_A/F_I and $PaCO_2$ for the five experiments.

$$p < 0.001, \ (F = 80.515, \ \Delta F_A/F_I = .00961 \cdot \Delta PaCO_2).$$


0.3
0.25
0.2
0.15
0.1
.05
0
0
2
4
6
8
10
12
14
△ ORIGINAL DATA
FITTED DATA
95% CONFIDENCE
△ F_A/F_i (SF_6-He)
△ P_sCO_2 (He-SF_6)

DISCUSSION

Our studies with gas density changes during high frequency oscillation support the analyses of Fredberg (1980) and Kurzweg et al., (1984) of gas transport. These analyses have variables which are dependent on the density, viscosity and kinematic viscosity of gases in the airways. Table 6 summarizes the physical properties of the inert gases used in these studies. The ratio of densities for SF_6-O_2 to He-O_2 in a 80%-20% gas mixture is 13.63. Figure 8 shows $PaCO_2$ and PaO_2 changes indicating that gas exchange is augmented with the denser carrier gas, SF_6-O_2. In the studies using 0.5% halothane (Figure 10) $PaCO_2$ was again found to be significantly less in the presence of SF_6-O_2 and PaO_2 greater as compared to He-O2. These changes in $PaCO_2$ and PaO_2 due to changes in gas density provide experimental evidence that inspired gas density, and/or kinematic viscosity may be important variables in the physiologic action of HFO, and that high density enhances gas transport while high viscoscity and kinematic viscosity impede gas transport with HFO.

Cardiac output was measured in our studies to insure that changes in alveolar uptake of halothane were not due to decreases in cardiac output. At concentrations of .5-.7% halothane, cardiac output did not change significantly with HFO at frequencies of 16, 25, and 34 Hz (Figure 9). Eger (1976) identified ventilation and cardiac output as two factors affecting the alveolar uptake of halothane. In contrast to the effect of ventilatory changes, a decrease in cardiac output elevates the alveolar concentration of halothane by retarding the uptake of halothane from the lung thus allowing the alveolar halothane to rise further. While F_A/F_I is an index of not only changes in ventilation but also in cardiac output, findings of others have indicated no changes in cardiac output at the concentration used in this

study. Using conventional ventilation Gibbons et al., (1977) found no significant difference in the F_A/F_I ratio with concentrations of .3 and 1.5% with ventilation held constant. From our measurements and from the studies of others cardiac output does not change with .5% halothane. Thus, any changes in F_A/F_I must be due to changes in ventilation.

A significant decrease in blood pressure from zero to seven minutes was found for both gas mixtures with .5% halothane (Figure 10). The blood pressure decrease appears to be independent of gas density because it occurred with both gas mixtures. According to Dripps et al., (1972) halothane decreases arterial blood pressure, myocardial contractile force, and heart rate. Figure 9 shows cardiac output during HFO at 16, 25 and 34 Hz did not change over a period of 0 to 7 minutes of .5% halothane administration. This data indicates the decrease in blood pressure measured during the halothane vs gas density studies was not due to a decrease in cardiac output. However, halothane does cause peripheral vascular dilation and this decrease in peripheral vascular resistance may account for the decrease in blood pressure measured during both SF_6-O_2-halothane and He-O_2-halothane.

In the halothane studies with He-O_2 and SF_6-O_2, the double exponential equation [14] similar to the one used for the frequency vs halothane uptake studies, was used to express the data. Additional constraints were added to the equation for the density studies to allow for improvement of fit of the data to the equation. The asymptotes for the equations using the F_A/F_I values for SF_6-O_2 were greater than the asymptotes for the F_A/F_I values for He-O_2. There was no such relationship with the time constants. The data for these experiments were taken from zero to ten minutes after the onset of the inspired halothane.

In the frequency vs F_A/F_I study (Figure 11) the data was collected over a twenty minute time period after the onset of halothane and a correlation between the frequency and time constants was observed. A possible explanation for the lack of correlation in the time constants for the density studies may be that the data was not collected over a long enough time period to make an accurate estimate.

Pooled data could not be legitimately fit to the model because of day to day or inter-animal variability. Others (Tanner, 1982 and Brandom et al., 1983) have similarly restricted themselves to fitting halothane uptake data to individual animals rather than pooling. For this reason the data was analyzed as shown in Figure 16. According to Daniel, (1978) when an event can result in only one of two mutually exclusive outcomes, it can be statistically analyzed using the binomial distribution. This analysis was used to answer the following question: "At any time after the onset of halothane administration with HFO at 30 Hz, is the arterial concentration of halothane with SF_6-O_2 equal to, or not equal to the arterial concentration of halothane with He-O_2?" The outcome of this analysis showed that the uptake of halothane with SF_6-O_2 was significantly greater than with He-O_2.

To account for the variability between experiments, the differences in the $PaCO_2$ for the two gas mixtures of each experiment were correlated to the differences in the estimated asymptote, B(1), and the differences in the F_A/F_I between the two gas mixtures (Figure 17 and Figure 18, respectively). There was a positive linear correlation indicating that as $PaCO_2$ differences increase between gas mixtures, the differences in F_A/F_I and B(1) increase. This correlation agrees with the work of others examining the alveolar uptake of halothane during conventional ventilation (Eger, 1976; Tanner, 1982; Brandom et al., 1983; Fukui and Smith, 1981b) which state that as ventilation

increases, as measured by a decrease in $PaCO_2$, the alveolar uptake of halothane (F_A/F_I) also increases.

The effect of inspired gas density on gas exchange has been measured with conventional ventilation. Worth et al., (1976) investigated the effects of 80% He, 80% N_2, 80% Ar and 80% SF_6, all with 20% O_2, on gas exchange in dogs with conventional ventilation using a frequency of 14 breaths per minute and a tidal volume of 217-276 ml. Tidal volume and frequency were held constant for each dog when inspired gas mixtures were changed. Gas density did not affect the stroke volume of the ventilator. There was no statistical difference in $PaCO_2$ or PaO_2 between the gas mixtures with conventional ventilation. However, the alveolar-arterial oxygen difference ($[P_A-P_a]O_2$) decreased significantly, indicating improved oxygenation with SF_6-O_2 compared to He-O_2. Worth stated that this finding may be due to an improvement in ventilation-perfusion distribution with the denser gas. Similar studies by Christopherson and Hlastala (1982) using 80% He 20% O_2 (HE-O_2) and air for inspired gas mixtures found that PaO_2 and $PaCO_2$ were not significantly different with the two gas mixtures but that $[P_A-P_a]O_2$ again decreased with the more dense gas mixture, air. Ventilation-perfusion distribution for the two gas mixtures was measured, but no significant difference was found to explain the decrease in $[P_A-P_a]O_2$ with the denser gas mixture.

Wood et al.,(1976) measured gas exchange in human subjects at one atmosphere breathing air or SF_6-O_2 and also found a significant decrease in $[P_A-P_a]O_2$ with increased gas density, but no significant change in PaO_2 or $PaCO_2$. Martin et al.,(1972) studied gas exchange in dogs with 80% N_2, 80% SF_6 and 80% He and 20% O_2 using conventional ventilation and again found no significant change in PaO_2 or $PaCO_2$ at one atmosphere. Although some unexplained improvement in oxygenation as measured by $[P_A-P_a]O_2$ has been

observed with a more dense inspired gas (Martin et al., 1972; Worth et al., 1976; Wood et al., 1976; Christopherson and Hlastella 1982), these studies indicate that gas exchange as measured by $PaCO_2$ and PaO_2 during conventional ventilation is uneffected by changes in gas density.

Drazen et al., (1984) considers two types of high frequency ventilation, each with different mechanisms of gas transport: one with small tidal volumes but larger than anatomical dead space and the other with tidal volume less than anatomical dead space. The anatomical dead space for 8-12 kg dogs as reported by Altman and Dittmer (1971) is 38-75 ml. The two types of high frequency ventilation may have different responses to changes in inspired gas density which, according to Drazen, can be explained by different mechanisms of gas transport. The latter type of high frequency ventilation is applicable to our studies because tidal volumes are 20-30 ml, a volume less than dead space. Robertson et al (1982) studied the influence of gas density on gas exchange using tidal volumes which appear to be larger than dead space. They ventilated dogs (17-27 kg) using a stroke volume of 105 ml and a frequency of 10 Hz.

The gas mixtures used in this study were 80% He, 80% N_2, and 80% Ar 20% O_2. The frequency and tidal volume selected represented the maximal frequency their device could deliver and maintain equivalent tidal volumes during gas density changes. The stroke volume produced by the apparatus with each of the three carrier gases was measured by filling a 2.7-liter capacity plethysmograph with the carrier gas and operating the HFO apparatus at 1-10 Hz with a tidal volume of 105 ml. Within this frequency and tidal volume range no differences in expelled gas volume from the ventilator could be measured with each of the three gases studied. No significant difference in gas exchange as measured by PaO_2, $PaCO_2$ or $[P_A-P_a]O_2$ was measured at a tidal volume of 105 ml

and frequency of 10 Hz with He-O_2, N_2-O_2, or Ar-O_2. These differences in results from our studies may be due to the higher tidal volumes, differences in measuring tidal volume, and the lower frequency used by Robertson et al (1982).

Solway et al., (1984) also examined the effects of gas composition in four dogs whose lungs were equilibrated with 80% He, 80% N_2, and 80% SF_6 20% O_2 during high frequency ventilation using a frequency range of 2-18 Hz and tidal volumes of 10-40 ml. The stroke output of the ventilator was neither measured nor changed for each gas mixture. CO_2 output was determined by the CO_2 concentration in the output gas flow times the bias flow rate which was held constant for all gas mixtures. Results showed no significant change in CO_2 output with density changes. These results of Solway et al. (1984) differ from the results of the present gas density studies. The frequency range of the Solway studies was 2-18 Hz, much lower frequencies than 30 Hz which was the frequency used in the present gas density studies. This variation in frequencies between the two studies may account for the differences in results.

In the studies by Robertson et al. (1982) and Solway et al., (1984) delivered stroke volumes were either measured and found to be constant or assumed to be constant with changes in gas density. In the present gas density studies tidal volume was estimated by measuring chest wall acceleration and changes in tidal volume were prevented when gas density was changed. These differences in methods for delivering and measuring tidal volume may account for the differences in results.

Solway et al. (1984) examined the effect of inspired gas density in the frequency range of 2-18 Hz and no differences in tidal volume at the airway opening was measured with gas density changes. Robertson et al., (1982) used a

frequency of 10 Hz and also measured no change in tidal volume during gas density changes. In the present studies using a constant stroke output at a frequency of 30 Hz, tidal volume, as measured by chest wall acceleration, decreased with an increase in inspired gas density as shown in Figure 5. Thus, variations in tidal volumes delivered during gas density changes were discerned in our studies.

At resonant frequency, because impedence in the airways is minimal, pressures at the airway opening, or airway opening pressures, are minimal. Watson et al. (1985) determined resonant frequency in 11 intubated dogs (7.9-12.7 kg) by measuring airway opening pressures during HFO in a frequency range of 5 to 40 Hz. The minimum airway pressure was measured at a mean ± SE frequency of 6.2 ± 0.6 Hz. Above this frequency mean airway pressures increased implying an increase in airway impedence. At frequencies greater than resonant frequency, inertial components begin to dominate the overall pulmonary impedence because the impedence of capacitance decreases inversely with frequency whereas the impedence due to inertance increases directly with frequency. At a frequency of 30 Hz, with inertance more significant, an increase in impedence with a more dense gas such as SF_6-O_2, will result in a decreased tidal volume delivered. Because inertance effects are significant at the higher frequency of 30 Hz, in the present studies tidal volume was estimated at the chest wall and changes in tidal volume were prevented when gas density was changed. These differences in tidal volumes and frequencies of the studies by Solway et al., (1984) and Robertson et al., (1982) and our studies may account for the differences in results.

Airflow profiles, whether oscillatory or not, can be described as a continuum with turbulent flow at one extreme and laminar flow at the other extreme. Fredberg (1980) developed the first model of quasi-steady turbulent

flow that made predictions for gas transport with high frequency oscillation. His mathematical model is as follows:

$$D_{axial} = D_{mol} + \varepsilon ud \qquad [15]$$

where D_{axial} is the axial diffusivity, which is most important to gas transport down the airway and gas exchange, D_{mol} is the molecular diffusivity, ε is a coefficient which is a function of Reynold's number, u is the velocity of flow, and d is the distance displaced.

According to Taylor (1953), during turbulent flow in smooth straight tubes, the coefficient ε is a function of the log of Reynold's number. Reynold's number, as may be recalled, is directly proportional to gas density and inversely proportional to gas viscosity. According to Fredberg, his formula of D_{axial}/D_{mol} may be applied to not only turbulent flow in straight pipes, but also more generally to flows in pipes that bifurcate, curve, or contain secondary flows. These more general types of flow are most likely present in the airways of dogs than flows present in straight pipes. If the term εud in equation [15] is significant in Fredberg's analysis, because ε is dependent on the Reynold's number which increases with an increase in gas density and decrease in gas viscosity, one would predict an increase in axial diffusivity with increased gas density. Thus, gas transport would increase with SF_6-O_2 as predicted by Fredberg's analysis.

To determine changes in ventilation with gas density as measured during our studies of gas exchange, $PaCO_2$ results presented in Table 3 were applied to the relationship between ventilation and $PaCO_2$ (West, 1981),

$$PaCO2 = \dot{V}CO_2/\dot{V}_{Ae} \cdot K \qquad [16]$$

where $\dot{V}CO_2$ is the CO_2 production, $\dot{V}_{Ae}$ is effective alveolar ventilation and K is a constant. We found an estimated 21% increase in ventilation with SF_6-O_2 compared to He-O_2. With this estimation, CO_2 production was assumed to be

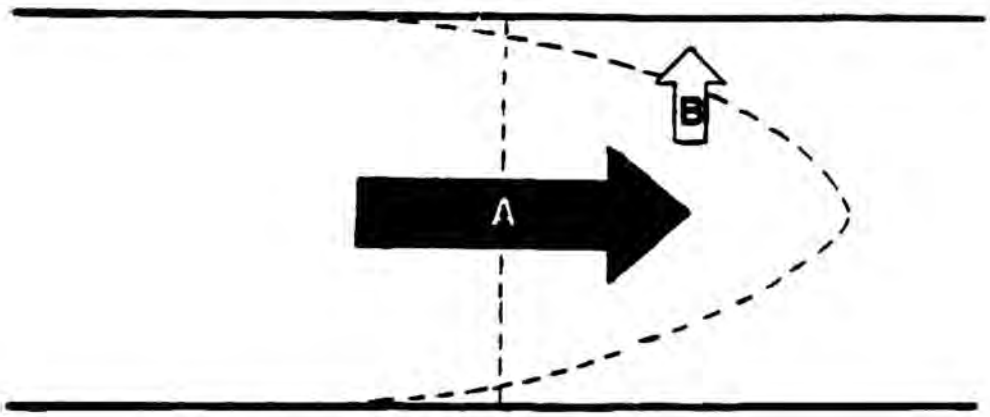
constant during the measuring of blood gases in our studies. The predictions of changes in axial diffusivities from Fredberg's analysis due to gas density is in the same direction as our estimation of effective alveolar ventilation ($\dot{V}A$). Thus, with the analysis of Fredberg (1980), gas transport should increase with increased gas density and decreased viscosity. The predictions of Fredberg (1980) agree with the results of the present study.

During laminar flow, gas transport may be explained by the phenomenon described by Taylor (1953), called Taylor dispersion, which examines the dispersion of material in a tube as a result of the interaction of the axial velocity profile and the radial concentration gradient during laminar flow (Figure 18). An increase in diffusivity of a substance is expected to lead to an increase in radial diffusion of that substance. Once a molecule diffuses out of the central velocity zone it will be retarded by the slower velocity at the periphery and cannot continue to move foward as rapidly as those molecules remaining in the central zone. With an increase in diffusivity the longitudinal spreading or dispersion will be impeded because an increase in radial diffusion will occur. Thus, a highly diffusible material disperses less rapidly in the longitudinal direction than one that has a low molecular diffusivity. Taylor showed that this dispersion process is inversely proportional to the molecular diffusivity.

The binary diffusion coefficients for oxygen and carbon dioxide in the different carrier gases estimated by Van Liew et al., (1982) are listed in Table 7. The tertiary diffusivities of halothane in 80% helium and SF_6 and 20% oxygen which were calculated for the present studies are listed in Table 8. The diffusivities range from 0.795 $cm^2 \cdot sec^{-1}$ for oxygen diffusivity in helium (Table 7) to 0.028 $cm^2 \cdot sec^{-1}$ for halothane diffusivity in SF_6-O_2 (Table 8). With a carrier gas of low density such as helium, in which O_2, CO_2 and

Figure 18. A schematic of the mechanism of Taylor Dispersion in laminar flow of the airways. Shown is steady laminar flow with dispersion of gas molecules by both radial diffusion and convective dispersion. The effect of radial diffusion reduces convective dispersion because the molecules in the central zone of higher axial velocity diffuse laterally to zones of lower velocity thereby impeding axial gas transport.

TAYLOR DISPERSION



A Convective Dispersion

B Radial Diffusion

Table 7. Binary Diffusion Coefficients ($D_{x,y}$) of O_2 and CO_2 in Helium and SF_6 at 37°C and one atmosphere. Calculated values obtained from Van Liew et al., (1982).

y	Units	$D_{O_2,y}$	$D_{CO_2,y}$
Helium	$cm^2 \cdot sec^{-1}$	0.795	0.651
SF_6	$cm^2 \cdot sec^{-1}$	0.0971	0.0751

$$D_{O_2,He} / D_{O_2,SF_6} = 8.18$$

$$D_{CO_2,He} / D_{CO_2,SF_6} = 8.66$$

Table 8. Tertiary diffusion coefficients of .5% halothane in 80% helium 19.5% O_2 ($HE-O_2$) and 80% SF_6 19.5% O_2 (SF_6-O_2) at 37°C and one atmosphere.

y	UNITS	$D_{halothane,\ y}$*
$He-O_2$	$cm \cdot sec^{-1}$	0.1886336
SF_6-O_2	$cm \cdot sec^{-1}$	0.0281161

$$D_{halothane,\ He,\ O_2} / D_{halothane,\ SF_6,\ O_2} = 6.75$$

* $D_{halothane,\ y}$ is the tertiary diffusion coefficient for .5% halothane in the gas mixture y, either 80% helium 19.5% oxygen, or 80% SF_6 19.5% oxygen.

halothane are more easily diffusible, the effect of Taylor dispersion is expected to be more pronounced, thereby leading to less effective gas transport in the airways. If flow is laminar, then the Taylor dispersion mechanism could explain our results indicating gas transport with HFO is inversely proportional to molecular diffusivity. If Taylor dispersion is significant with HFO one would predict an increase in gas transport with gases of low diffusivities such as halothane in SF_6. These predictions for laminar flow are also in agreement with our findings. At this time it is unclear in our studies whether flow is turbulent or laminar during HFO. The analysis by Kurzweg and Jaeger (1984), suggests that the process of gas transport with HFO may in large part be due to laminar dispersion which is directly dependent again on the Womersley number. Both models predict that with an increase in kinematic viscosity, there is a decrease in gas transport. That is, with $He-O_2$, which has a higher kinematic viscosity, gas transport is less efficient than with SF_6-O_2 as measured by the transport of O_2, CO_2, and halothane. Thus, the results of the present studies are consistent with the analyses of Fredberg (1980) and Kurzweg, Howell and Jaeger (1984).

CONCLUSION

The present data indicate that, in contrast to conventional ventilation, gas exchange during high frequency oscillation is dependent on the gas density and as gas density increases, the efficiency of gas exchange increases as measured by PaO_2, $PaCO_2$, and the alveolar uptake of halothane. The inspired gases used in the present study not only differ in density but also in kinematic viscosity and molecular diffusivity. The observation that gas exchange during HFO at 30 Hz using tidal volumes less than dead space improves with SF_6-O_2 suggests that gas exchange is proportional to density and inversely proportional to viscosity, kinematic viscosity and molecular diffusivity. These findings provide evidence that gas exchange with HFO, in contrast to conventional ventilation, is more dependent on mechanisms which are influenced by these physical properties. Our studies are not able to determine which of these physical properties are of most significance to the mechanism of gas transport with HFO.

The model of Fredberg (1980) theorizes that gas flow with HFO is turbulent. According to Fredberg, gas exchange is dependent on Reynold's number which is proportional to density. Thus, the predictions of this analysis are in agreement with our data.

On the other hand, if gas flow with high frequency oscillation is laminar, our results could be explained by the Taylor dispersion mechanism which states that axial gas transport is enhanced by a decrease in molecular diffusivity. According to West (1981) existing evidence appears to suggest that this mechanism is of little relevance to the mechanism of gas transport with conventional ventilation and normal breathing. In contrast, the present studies suggest that if flow is laminar with HFO Taylor dispersion may be significant. A diagram describing Taylor dispersion is shown in Figure 18.

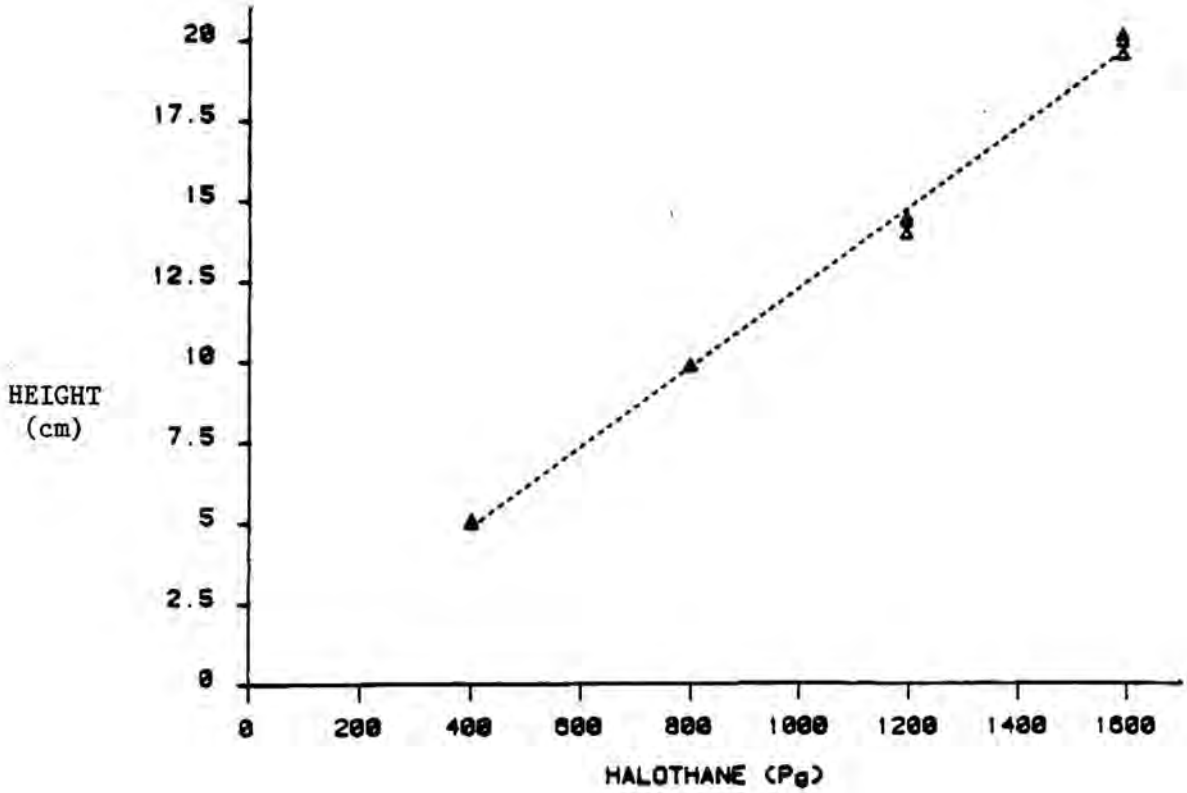
In summary these results contribute experimental evidence to develop and refine analyses of gas exchange with high frequency oscillation. This observation that gas transport with HFO is dependent on the physical properties of the inspired gas mixtures more fully explains the mechanism of ventilation and gas exchange during HFO. The understanding of such factors brings us closer to a complete and applicable description of gas exchange with high frequency oscillation.

Appendix I: Calibration of the gas chromatograph using known concentrations of halothane and measuring peak heights.

Pg = picograms

cm = centimeters

Correlation coefficient = .99805, n = 10.


HEIGHT
(cm)
20
17.5
15
12.5
10
7.5
5
2.5
0
0
200
400
600
800
1000
1200
1400
1600
HALOTHANE (Pa)

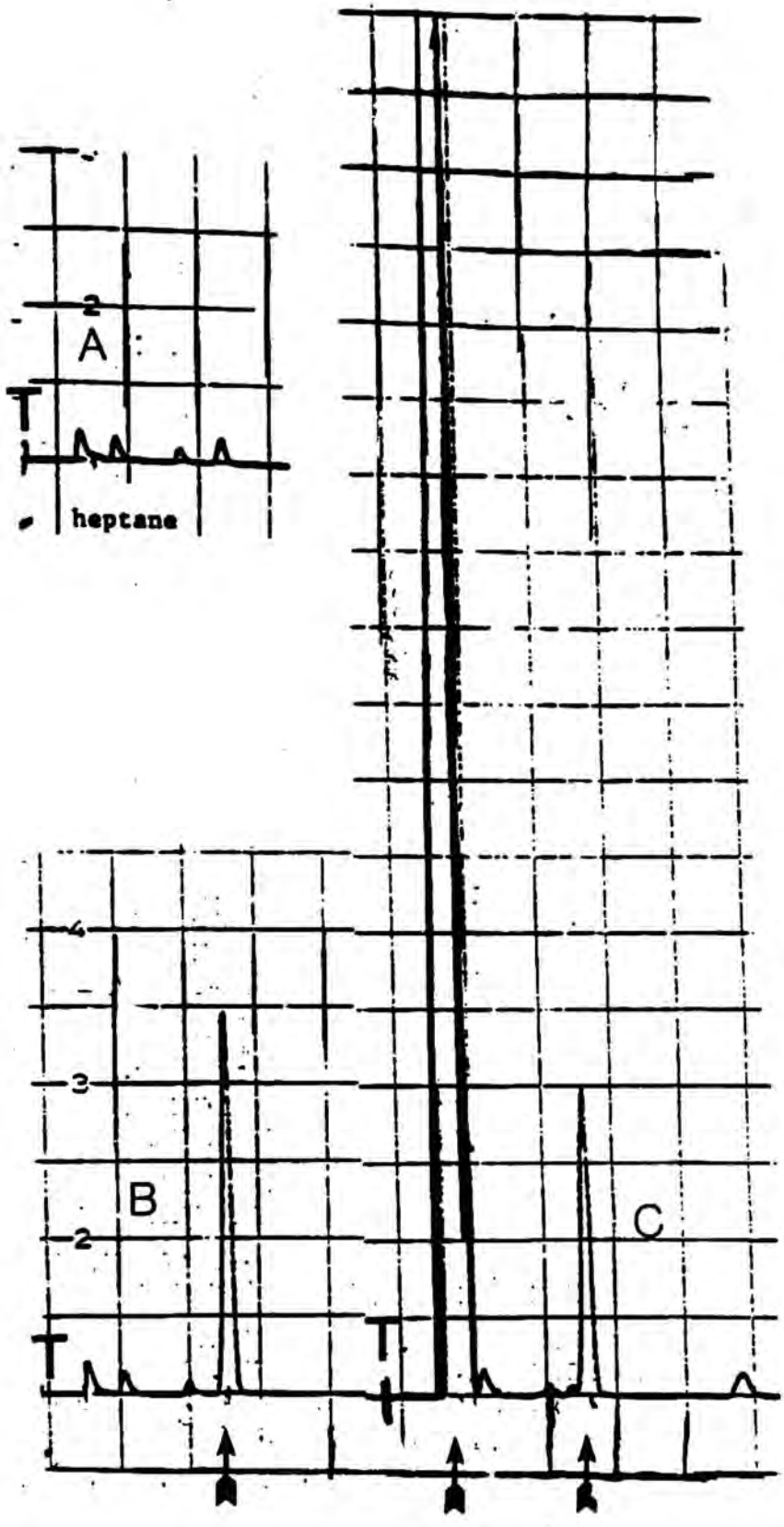
Appendix II: Separation peaks for halothane and SF_6 using gas chromatograph. Chart speed is equal to one centimeter per minute. The halothane peak occurred two minutes after the SF_6 peak and even with a very large amount of SF_6, the peaks were separate.

A = heptane

B = heptane and halothane

C = SF_6, halothane and heptane

T = time of sample injection


2
A
heptane
4
3
B
2
C
halothane,
SF6
halothane,

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