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AEROMEDICAL REVIEWS

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Review 4-62

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USAF SCHOOL OF AEROSPACE MEDICINE
AEROSPACE MEDICAL DIVISION (AFSC)
BROOKS AIR FORCE BASE, TEXAS

PATHOGENIC MECHANISMS IN GAS AND FAT EMBOLISM

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Review 4-62

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PATHOGENIC MECHANISMS IN GAS AND FAT EMBOLISM

The syndromes produced by gas and fat emboli constitute a problem area in clinical medicine. Often, the symptomatology is nonspecific; the diagnosis difficult; the treatment insufficient; the results disastrous. Likewise, such embolism is of considerable interest and importance to the physicians serving aviators, divers, and caisson workers. These individuals are exposed to changes in barometric pressure that often produce symptoms similar to those seen in gas and fat embolism. These syndromes, called *dysbarism* or *decompression sickness*, are thought by many to have an etiology involving gas and fat emboli.

Much has been written about "pure" gas embolism, "pure" fat embolism, and dysbarism; less attention has been given to their similarities. This review was written to discuss and compare these forms of embolism, with emphasis given to the circulatory pathways by which the emboli can be distributed. Knowledge of the general mechanisms in the transport of emboli could lead to a better understanding of the etiology and pathogenesis of all these syndromes; at least, it can provide a firm base for hypotheses to be tested in searching for etiologic mechanisms.

FAT EMBOLISM

Clinical aspects

The presence of intravascular fat droplets is much more common than is generally suspected; such occurrences are seldom recognized. Davis and Musselman (17) state that one-half of all persons who have been moderately or severely injured have some degree of fat embolism and that in 10% of this group death is the result. Several studies have shown that the incidence of pulmonary fat embolism in routine hospital autopsies is about 30% (table I).

TABLE I

Types of patients in whom pulmonary fat embolism was sought, and its incidence and severity

	Number of persons	Degree of fat embolism				Percentage incidence of fat embolism
		None	Mild	Moderate	Severe	
Battle casualties	14	2	4	6	2	86
Civilian casualties	19	2	6	4	7	89
Routine hospital autopsies:						
Medical	72	62	7	3	0	14
Surgical	28	18	6	3	1	36
Children	25	25	0	0	0	0
Total	158	109	23	16	10	31

Reprinted by permission from Whiteley (65).

In World War II, the Committee for the Study of the Severely Wounded found fat emboli in the lungs of 65% of patients dying after battle wounds. Peltier (45) mentions several studies showing the seriousness of the problem in civil life: fat embolism appears to be the direct cause of death in 5% of patients dying with long bone fractures. The clinical syndromes have been conveniently classified by Sevitt (55). He differentiates pulmonary and systemic forms, and subdivides systemic forms into: (1) the fulminating type, (2) the classical or full syndrome, and (3) incomplete or partial syndromes.

The pulmonary embolism is the most common form and the least serious: most cases are unrecognized, as shown by the high incidence at autopsy, mentioned above. This presumably reflects the large reserves of the lungs; Sevitt considers trapping of emboli by the lungs as physiologic rather than pathologic, and regards pulmonary congestion, edema, small hemorrhages, and foci of collapse in the lungs as due to nonembolic causes. However, heavy pulmonary deposits of emboli are closely related to profound shock. Murray (43) proposes that the shock itself is primary, and that fat embolism may be secondary to it (via a "fat center" in the hypothalamus).

Cases of the fulminating systemic type are seen after severe and multiple injuries, with onset within a few hours to one day after injury; they are characterized by bizarre cerebral signs (which may be unilateral, bilateral, or generalized) accompanied by shock, oligemia, and hemorrhage. Death occurs within one to three days.

The classical syndrome is characterized by major cerebral effects, respiratory symptoms (with signs of dyspnea, moist rales, cough, sputum, and even pulmonary edema), pyrexia, tachycardia, and a characteristic petechial eruption of much diagnostic importance. The first symptoms occur within 24 to 48 hours — often suddenly. Shock is not a common part of this syndrome, unless oligemia is untreated or terminal cardiac failure ensues.

Incomplete and partial syndromes include:

1. Symptoms representing the classical picture, but without the respiratory signs.
2. Respiratory distress, pyrexia, tachycardia, and rash, but no cerebral symptoms.
3. Symptoms listed, except for significant cerebral or respiratory signs.

Systemic embolism does occur asymptotically. In a series of 100 necropsies at the Birmingham Accident Hospital (55) on patients not suspected of having clinical embolism, systemic embolism and pulmonary embolism were found in 24% and 89%, respectively. In every case of the former, the latter was also present.

Mortality is highest in patients having cerebral symptoms.

Pathophysiology

It is generally agreed that the essential feature of fat embolism is the presence, in the circulating blood, of fat globules large enough to occlude arteries and capillaries (44); the globules then lodge, producing effects through mechanical and chemical action. The source of the fat globules is debated. In cases of embolization after fractures of long bones, it has generally been thought that bone marrow fat contributes to the intravascular fat emboli. Lehman and Moore (36), in 1927, first expressed doubt that there is enough fat in the bones to be the sole cause of the clinical signs. Also, clinical fat emboli may be seen after injuries in which there is no fracture (59), or even in the absence of physical trauma, as in the cases of neurocirculatory collapse of dysbarism. Peltier, in extracting fat from long bones with hot alcohol, obtained much more than did Lehman and Moore, but noted that it was still conjectural whether quantities of fat of the magnitude his group found would prove fatal upon entering the circulation in man (45). Swank and Dugger (59) agree with Lehman and Moore that the

source of emboli is probably not bone or depot fat by itself. Their studies with dogs prompted the suggestion that freely circulating fat globules are present normally, especially in conjunction with alimentary lipemia. LeQuire and co-workers (37) made observations at necropsy and performed animal experiments which led them to doubt that depot fat is the primary source of embolic fat, but rather to suspect that the source is aggregation of blood lipids resulting from a deficiency or inactivation of plasma emulsifiers. They suggest that while fat from traumatized depots may enter the circulation on occasion, this process in itself is not the only mechanism involved, and the tissue injury, associated with shock, initiates physicochemical alterations which result in colloidal instability of plasma lipids, giving rise to lipid aggregation. This hypothesis was based on the finding that fat emboli in the lungs of nine patients having a histologic diagnosis of fat embolism, and in the lungs of rabbits exposed to decompression, contained at least 10 to 30% cholesterol. Since depot fat contains less than 1% cholesterol (37), they concluded that other sources must be important. Whiteley (65) disagrees, stating that from his own experiments with rats, there was no evidence to support the view that fat emboli would be derived from clumping of the chylomicrons, nor did alimentary lipemia contribute to the degree of pulmonary fat embolism. He points out that Young and Griffith (67) have satisfactorily demonstrated, with a hydrostatic model, the ease with which intravasation of emboli (through diapedesis) into the general circulation can occur whenever extravascular (tissue) tension exceeds intravascular pressure. Whiteley goes on to propose a dual, reciprocal relation between tissue injury and fat embolism; not only does fat enter the circulation from the locality of the injury, but the injury itself modifies the (pulmonary) vascular bed, making it more sensitive to the presence of intravascular fat. Davis and Musselman (17) agree with this view, stating that under conditions of stress, high concentrations of lipids and lipase may liberate excessive fatty acids, destabilizing the chylomicron emulsion and the formed elements in the blood. Murray (43) explains the source of the high concentrations of lipid in injuries on the basis of a "fat center" in the hypothalamus, which, when stimulated by such stresses as shock, severe illness, and trauma, mobilizes fat (as total circulating lipid).

Whatever their source, once the fat globules have formed, they probably pass slowly through the capillary beds of the body and usually most of them are held in the capillary beds of the general circulation. Swank and Dugger (59) state that the lungs function as a filter, and normally prevent "showers" of fat emboli to the brain and rest of the body. The early onset of cerebral symptoms of fat embolism, he suggests, is secondary to shock, unconsciousness, or anesthesia — any of which may relax the pulmonary vascular bed and allow the globules to be "washed through" (they do not specify which portion of the vascular bed is relaxed). Peltier cites work (23) that demonstrated fat emboli in the lungs of rabbits within seconds after fracture of the femur. This finding, he states, "precludes the possibility of any other avenue" of embolization to the lungs than via the great veins and right heart. In an extensive literature review (45), he cites many authors in proposing this pathogenesis of the various forms of fat embolism: the acute, fulminating type, dominated by severe shock, is due to acute failure of the right ventricle due to the mechanical blocking of the pulmonary vessels by the emboli; the classical syndrome, with its attendant latent period, represents the time lag between the lodgment of emboli of neutral fat within the pulmonary vessels and the hydrolysis of sufficient fatty acids from this neutral fat to produce local hemorrhagic effects. "The role of embolic fat in cases of fat embolism with the classical clinical signs and symptoms is a chemical one, associated with the hydrolysis of neutral fat and the release of free fatty acids," he concludes. Whiteley (65), noting that the larger and fewer the emboli, the more serious the clinical state, suggests that the bronchopulmonary venous shunt (described by Marchand et al. (41)) may be set into action, allowing large emboli to pass into the systemic circulation. LeQuire's group (37) agree with this theory of increased pulmonary artery pressure and attendant vascular atony. They note that fat injected intra-arterially traverses peripheral vascular beds, while embolic fat released from the lung will localize in these beds; thus physicochemical alterations in the aggregates enhance their ability to stick and build up in capillary beds subsequently encountered. This view is supported by Peltier et al. (44), who, after demonstrating the rise in serum lipase in cases of long bone

fracture, state that "the elaboration of the serum lipase following trauma to bone is due to an increase in the lipase secretion of the lung parenchyma as a response to the presence of multiple emboli of neutral fat."

To explain the clinical syndromes, Davis and Musselman (17) propose that the systemic emboli produce damage not only from interference with blood flow, but perhaps also from the effects of the products of fatty hydrolysis and metabolism at the site of occlusion. Thus, capillary plugs of the formed elements of the blood may be produced as a result of surface alteration producing an active adhesion between formed elements and vascular walls, this adhesion being a result of the destabilization of the formed elements from excessive concentrations of serum lipids and lipase.

Peltier (45) divides the deleterious effects of the emboli, describing an initial stage of mechanical obstruction of the pulmonary vascular bed, and a second stage of chemical disruption of the pulmonary capillary endothelium, due to the hydrolysis of neutral fat which releases fatty acids. The fatty acids then lead to dyspnea, disorientation, and petechial hemorrhages. Peltier goes on to explain that the free fatty acids produce these effects by chemical action on the endothelium; that fatty acids have a marked affinity for calcium ions, and the dissolution of the capillary walls may be due to the immobilization of calcium ions as soaps of the fatty acids at the intercellular junction. Work is mentioned which demonstrates that calcium ions are essential for intercellular cohesion, and when these ions are removed the endothelial continuity is easily disrupted.

GAS EMBOLISM

Clinical aspects

This discussion includes syndromes thought to be produced, at least in part, by gases evolved from solution in the body, as well as those disastrous events occurring when quantities of ambient air or other gases are introduced into the blood stream, as in some cases of pneumothorax, obstetric procedures, or venipuncture.

Evolved gas syndromes form a group of diseases to those employed in aviation, underwater construction, and diving (22), all of whom are liable to the symptom complex known as *dysbarism*. Adler (2) defines dysbarism as those syndromes, exclusive of hypoxia and airsickness, consisting of those disturbances in the body resulting from the existence of a pressure differential between the total ambient barometric pressure and the total pressure of dissolved and free gases within the body tissues, fluids, and cavities. Thus, dysbarism can occur in persons exposed to high pressure, then coming to atmospheric pressure (as in caisson workers), or in persons proceeding to and from reduced barometric pressure (27). Dysbarism syndromes are usually classified according to two chief mechanisms: evolution of dissolved gases from solution, and the expansion of trapped gases. The latter will be mentioned only briefly, inasmuch as evolved gases, the subject under discussion, are not thought to play a prominent role, if any at all, in their production. The trapped gas syndromes, then, are due to expansion of gases within closed cavities (either real or artificial), causing symptoms by mechanical (pressure) effects. They include: abdominal distension, aerotitis media (air trapped in the middle ear); aerosinusitis; aerodontalgia, and other less common symptoms. This group accounts for about 70% of the cases of dysbarism.

The evolved gas syndromes are those thought to be produced by evolution of bubbles from gas normally in solution. They include: bends, chokes, skin manifestations, and neurocirculatory collapse. Bends are pains in the joints, bones, or muscles, usually deep, diffuse, and poorly localized. Of these, 54% have been recorded as joint pains, 26% as muscle pains, and 26% as pain deep in the bone (13). Chokes are characterized by a boring, constricting substernal distress, a dry cough, and dyspnea; these symptoms are aggravated by attempts to take a deep breath (2). The skin manifestations of dysbarism are varied—sometimes cyanotic mottling is seen (a serious prognostic sign) (9), and sometimes only subjective sensations such as pruritus or feeling hot and cold (12), are present. Occasionally, subcutaneous emphysema is seen (2). Neurocirculatory collapse is a severe form of dysbarism, but its etiology is obscure. It includes varying degrees of cerebral

symptoms, usually bizarre, including scotomata, paralysis, and aphasia, as well as cardiac syndromes resembling acute angina, acute heart failure, thrombosis, syncope, and shock. Many persons develop these symptoms secondary to another form of dysbarism (it is seen in 10% of severe bends and 25% of chokes) (1). Some cases may have the onset of these symptoms several hours after recompression. Berry (9) has made the following classification of patients suffering serious reactions:

Group 1: Persons having such initial symptoms as bends, chokes, or gas, followed by syncope or signs of impending syncope, with recovery by the time ground level is reached.

Group 2: Persons having circulatory and other autonomic signs and symptoms at altitude, who recover at ground level within two hours, and then have a subsequent delayed reaction.

Group 3: Persons having circulatory and other autonomic signs and symptoms at altitude which progress to immediate or delayed shock.

Group 4: Persons having syncope without preceding symptoms.

Group 5: Persons with any of numerous neurologic signs and symptoms who either proceed to recovery or have residual defect.

About 52% of cases fall into group 1, with 38% in group 5. Of the various evolved gas syndromes, bends are by far the most common, occurring 5 to 8 times as often as chokes (13). Neuro-circulatory collapse is seen in about 5% of serious dysbarism cases, occurring in about 0.04% of all persons exposed to an altitude of 30,000 feet or more (1). Reports of fatality range from 1 in 40,000 to 1 in 80,000 persons exposed in altitude chamber runs (53).

Of interest is the fact that venous and arterial gas embolism from causes other than reduced barometric pressure give rise to the same types of syndromes as those seen in dysbarism (10, 20). Air emboli directly enter the veins after artificial pneumothorax and other thoracic therapeutic procedures (20). Various central nervous system signs, including strabismus, convulsions, vascular collapse, marbling of skin, and air bleeding have been noted after artificial pneumothorax. Rangell (51) reviews the long history

of air embolism as a complication of various obstetric procedures. These also are dominated by circulatory collapse, respiratory difficulties, and bizarre cerebral signs.

Pathophysiology

The many theories proposed regarding the etiology of the dysbarism syndromes indicate the lack of specific evidence. Among the mechanisms proposed have been intravascular and extravascular evolved gases, fat emboli, autonomic nervous system collapse, sludged blood, and vasospasm, alone or in combination (8). The largest body of evidence has been in favor of evolved gas bubbles as the primary agent; the possible role of other mechanisms is outside the scope of this paper. An excellent review of these alternate proposals is given by Adler (2).

There is considerable evidence that gas bubbles appear within the blood vessels after suitable exposure to reduced barometric pressure. Armstrong (3) was the first to show that this occurred after ascent to high altitude, although as early as 1690, Robert Boyle had noted a bubble in the eye of a viper exposed to high vacuum. Recent work has clearly shown that air emboli do indeed occur in the arteries, veins, and extravascular areas of various animals upon decompression. Harvey and co-workers (26), in a comprehensive experimental and theoretic study, have elucidated the mechanics of gas bubble formation in vivo. They describe the tendency for a gas to form bubbles by coming out of solution, expressing this tendency as the total tension of the gas in the medium minus the absolute pressure; that is, a positive pressure differential must exist. Also called into play are gas nuclei, or minute invisible spheres of gas already present prior to decompression; the original source of these nuclei remains unknown. Armstrong (3) found the composition of the gas bubbles in the right ventricle to be approximately 60% nitrogen, 28% carbon dioxide, and 11% oxygen; in the jugular vein, the composition was measured as approximately 65% nitrogen, 28% carbon dioxide, and 7% oxygen. Since theoretic calculations show a lower concentration of CO₂, it has been suggested that the negative pressures used to obtain the samples in Armstrong's experiments

added CO₂ to the gas bubbles from dissolved CO₂ (35). Most workers think that evolved gas bubbles always, or nearly always, form only on the venous side of the circulation, because the hydrostatic pressure of the arterial circulation works against bubble formation, and also because nitrogen, the main component of the emboli, is easily breathed out in the pulmonary circulation (12, 13).

Malhotra and Wright (40) have suggested, on the basis of data from rabbit experiments, that in the case of explosive decompression, arterial embolism occurs directly into the pulmonary venous circulation and that it is due to overdistension of the lungs, presumably through rupture of ambient air into the pulmonary capillaries.

Pathologic findings indicate that air emboli produce these syndromes through mechanical obstruction, at least in the non-dysbaritic cases. Rangell (51) cites several authors who have found such evidence as frothy blood in both the cerebral arteries and veins of obstetric patients dying of symptoms of air embolism (named above). Likewise, air emboli are regularly found in the cerebral vessels of rabbits and dogs after rapid decompression; Bohorfoush (10) and Durant et al. (20) describe the finding of air emboli in the coronary and cerebral circulation in deceased patients who had showed these signs after thoracic procedures.

Direct evidence on the effect of emboli on the central nervous system has been provided by Swank and Hain (58). Paraffin emboli ranging from 4 to 60 μ in size were injected into the arterial circulation of dogs, producing microscopic infarcts in the brain; small emboli were found in the white matter; larger ones were found in both gray and white matter. The authors state that the lesions produced were a product of severe ischemic anoxia resulting from temporary blockage of the vessels, and that vessels walls remained intact. This observation correlates with the pathologic findings in the human patients discussed above.

There is little direct evidence of the production of new gas bubbles in humans suffering from dysbarism. As Chubb (12) states, "this is not surprising, since the fatal cases are not examined prior to recompression." Good indirect evidence is found

in the fact that denitrogenation protects persons from dysbarism, and that recompression has recently been shown to be highly successful in relief of symptoms and signs of dysbarism (15). Johnson (30) performed autopsies on the bodies of patients dying of dysbarism, with the cadavers under water, in an attempt to identify gas bubbles. His study yielded indifferent results.

CIRCULATORY ASPECTS

One difficulty in the explanation of the syndromes of gas and fat embolism is elucidation of the means by which the emboli are transported to the brain, the coronary circulation, and other sites where severe pathologic conditions have been observed. In air embolism, following pneumothorax and rapid decompression, air is assumed to enter the pulmonary vein and, thus, the arterial circulation directly. In the other syndromes, for instance neuro-circulatory collapse of dysbarism, some means of transport must be present, since the pulmonary capillaries are thought to act as a filter to the venous side (59), where the bubbles are formed. Likewise, in fat embolism, a mechanism of transport to the arterial side from the site of production (at least in trauma) must be considered, unless and until it is proved that fat emboli are indeed formed from circulating lipids. The following discussion concerns possible circulatory pathways of embolism.

Arteriovenous anastomoses

The term *arteriovenous anastomoses* is used here to mean normally existing microscopic channels, other than capillaries, between arteries and veins. Unlike those larger abnormal channels of the same name which are the result of trauma or vascular neoplasms, these microscopic channels are not generally familiar to medical workers. Their existence has been known since the middle of the nineteenth century, as amply recorded by Clark (14) in his extensive review of the literature through 1938; more information about their structure and function has become available in recent years.

These anastomoses (hereafter called AVA) first gained acceptance as a normal occurrence in mammals in 1924, when Masson (42) demonstrated the source of the glomus tumor to be the tufts of AVA occurring in the pads of fingers and toes. Later, the AVA were shown to occur throughout the skin of man and other mammals. Recently, AVA have been demonstrated and studied in such tissues as the nose and visceral organs of humans, rabbits, rats, and dogs (5, 18, 24, 25, 32, 47, 48, 56, 60, 63, 64). Various methods have been employed; among these have been injections of various materials into the blood vessels (19, 48), histologic examination of the tissues (34), and microscopic and x-ray observation of the living organs (49, 54).

Prinzmetal and co-workers (48), by injecting small glass beads of known size into the arterial supply of various organs and recovering them from the veins, have had good results. This group has demonstrated AVA in the human heart, stomach, lung, and kidney; and the liver, spleen, lung, and kidney of rabbits and dogs. They conclude that there is a universal occurrence of AVA in the body. Others disagree, notably Gordon and co-workers (25). The latter group employed a method based on the interfacial tension between two immiscible liquids or gases, and concluded that in most visceral organs there are no AVA, or else they are much smaller than those proved to exist in the periphery of the body. Their results are presented in table II.

There are many differences of opinion concerning the size of these vessels. Prinzmetal's results, shown in table III, have been criticized because the pressures used are thought, by some, to be so high as to produce false passages and thus erroneous figures. Law (34), in a histologic study, estimates the AVA of human skin to be 40μ in diameter. Saunders and James (54), employing an x-ray microscopy technic, found the skin AVA to be markedly variable in size, but averaging 40μ at the arterial end and 60μ at the venous end.

Clark states that the AVA behave in much the same way as arteries and arterioles, except that they are decidedly more active and tend to behave independently by contracting and dilating

TABLE II
Results of perfusion studies of A-V vessels in the rat

Perfusing fluid	From	To	Internal diameter of largest A-V vessels (μ)			Number of experiments
			Min.	Max.	Av.	
Air	Aorta	Iliac veins and vena cava	32.8	45.0	39.0	3
Air	Aorta	Mesenteric veins	14.0	14.9	14.6	4
Air	Pulmonary artery	Pulmonary veins	15.4	16.6	16.0	2
Air	Aorta	Renal vein	12.7	17.3	14.2	16
Air	Portal vein	Hepatic veins and vena cava	25.8	41.6	34.1	21
Air	Aorta	Portal vein	19.6	25.8	22.2	7
Mercury	Aorta	Iliac veins and vena cava	41.0	64.3	53.9	3
Mercury	Aorta	Renal vein	18.8	25.0	21.7	8
Kerosene	Aorta	Renal veins	11.5	11.8	11.6	3

Reprinted by permission from Gordon et al. (25).

TABLE III

Determination of the size of arteriovenous anastomoses in the organs of various animals, by perfusion of glass spheres

Animal	Organ studied	Injection site	Tissue in which spheres were recovered	Diameter of largest sphere recovered (μ)
Rabbit 1	Liver	Portal vein	Lungs	60
Rabbit 2	Liver	Portal vein	Lungs	80
Rabbit 3	Liver	Portal vein	Lungs	70
Rabbit 4	Liver	Portal vein	Lungs	180
Rabbit 5	Liver	Portal vein	Lungs	150
Rabbit 6	Liver	Portal vein	Lungs	160
Rabbit 7	Liver	Portal vein	Lungs	0*
Rabbit 8	Liver	Portal vein	Lungs	120
Rabbit 9	Liver	Portal vein	Lungs	170
Rabbit 10	Liver	Portal vein	Lungs	50
Rabbit 11	Liver	Portal vein	Lungs	170
Dog 1	Spleen	Splenic artery	Liver	370
Dog 2	Spleen	Splenic artery	Splenic vein	160
Dog 3	Spleen	Splenic artery	Splenic vein	170
Dog 4	Spleen	Splenic artery	Splenic vein	170
Dog 5	Spleen	Splenic artery	Liver	200
Rabbit 12	Lungs	Right ventricle	Liver	230
Rabbit 13	Lungs	Pulmonary artery	Liver	160
Rabbit 14	Lungs	Pulmonary artery	Liver	290
Rabbit 15	Lungs	Pulmonary artery	Liver	190
Rabbit 16	Lungs	Marginal ear vein	Liver	160
Rabbit 17	Lungs	Marginal ear vein	Liver	190
Cat 1	Lungs	External jugular vein	Liver	390
Dog 6	Lungs	Pulmonary artery	Liver	100
Dog 7	Lungs	Pulmonary artery	Liver	180
Dog 8	Lungs	Pulmonary artery	Pulmonary vein	160

*No spheres recovered.

Reprinted by permission from Prinzmetal et al. (48).

spontaneously and rhythmically. Since that time, more evidence concerning the activity and control of the AVA has appeared; recent work on the hemodynamics and regulation of AVA indicates they have an active and important role in the microcirculation (4, 29, 52, 68, 69).

The existence of AVA in the lungs is of particular interest, for if present they would provide a direct route by which emboli could pass into the systemic circulation from the venous side. Several authors are convinced of the existence of AVA in large numbers in the lung. Von Hayek (62) estimates that, on the basis of the width and estimated total number of AVA, one-tenth the amount of blood in the pulmonary circuit can pass through them; either bronchial arterial blood or pulmonary arterial blood can flow through them to the pulmonary veins, depending on which portion of the "Sperr" arteries, or connecting branches between bronchial and pulmonary arteries, are contracted. As noted in table III, Prinzmetal suggests that their size is up to 290 μ in the rabbit, 180 μ in the dog, and 390 μ in cats; while Gordon and co-workers state that the lung AVA are no larger than 25 μ internal diameter. Kniseley et al. (31) have done considerable work on this subject; in experiments with bead injection, no beads were recovered if the thoracic portion of the inferior vena cava was ligated, suggesting that retrograde flow, not lung passage, might account for the finding of beads in terminal organs. Elsewhere, Kniseley has stated that "my own feeling is that the largest channels in healthy lungs are around 20 μ " (52). Rahn and co-workers (49) injected beads through catheters lodged in the pulmonary conus of anesthetized dogs, and recovered beads of 200 μ diameter in one of twelve dogs. Tobin and Zariquiey (60) recovered glass spheres averaging 37.5 μ from fresh human lung perfused with spheres in saline at 50 to 300 mm. Hg pressure; on dissection, the pulmonary veins yielded spheres up to 500 μ in diameter.

Villaret and Cachera have shown that air embolism from the peripheral veins can cross the lung, become arterialized, and produce visceral and cerebral disorders (61). In 1939, Etienne and Andre Curtillet from experiments on rabbits, concluded that

air cannot pass capillaries with a caliber less than 30μ (16). They, therefore, assume that in the lungs there are communications larger than 30μ , either AVA or particularly large capillaries.

Bergstrand (7) points out that the controversy concerning air passage through pulmonary capillaries probably exists because air is rarely found in the left half of the heart after death. This, he states, is quite natural, since there is no impedance to the emboli once they reach the left heart. He records personal observation of air bubbles circulating in the exposed carotid artery of experimental animals for 25 minutes, and air emboli getting stuck in the choroid arteries for more than one hour, after injection of air.

Patent foramen ovale

Interest has been shown in this possible mechanism for the shunting of embolus-laden blood from right to left since Haymaker et al. (27) found anatomically patent foramina ovale in two fatal cases of decompression sickness. It is thought that greatly increased pulmonary artery pressure, caused by blockage of the lung capillaries by emboli, leads to a right-to-left shunt. Normally, the right ventricular pressure is considerably lower than the left ventricular pressure, so the shunt does not function. Anatomically, patent foramen ovale occurs in 20 to 25% of adults (21); thus, in one-quarter of persons, emboli could reach the arterial side by this route alone. However, Lamb (33) states, "Insofar as decompression sickness is concerned, or possibility of fat emboli, or the release of nitrogen bubbles from fatty tissue, it is not necessary to postulate the presence of an atrial septal defect for their occurrence. There are abundant quantities of fatty tissue within the central nervous system itself and such tissue is heavily saturated with nitrogen. Direct release of nitrogen substances from the fatty tissue within the central nervous system is capable of causing neurologic disturbances without an embolus having to be transmitted across the septal defect."

Vertebral venous system

This system consists of the epidural veins, the paravertebral veins, the thoraco-abdominal wall veins, those of the head and neck, and the vena vasorum of the extremities, all in valveless connection with one another. This system, first described by Batson (6), parallels, connects with, and provides by-passes for, the portal, the pulmonary, and the caval systems of veins, and hence can provide in itself a pathway for the spread of emboli between remote organs. Batson suggests this pathway in air embolism, stating that "introduction of air into these veins would account for the blindness and even death which sometimes follows the diagnostic perirenal insufflation of air or air injections to produce pneumothorax." He cites a case where, at autopsy, air was found in the large dural sinuses only, and suggests that anoxia from the air emboli, blocking the rolandic veins, seems to have been the cause of death. Rait (50) also mentions this route as one by which embolism can occur in dysbarism.

Bronchopulmonary venous shunt

This circulation has been studied extensively in recent years, especially in reference to pulmonary hypertension from various causes. Marchand and co-workers (41) studied the anatomy of the bronchial vasculature by injecting vinylite of various colors into the vessels of normal lungs. They found a rich communication network between pleuro-hilar bronchial veins and the pulmonary veins. Every lung injected through the bronchial veins showed free filling of pulmonary veins. This group concluded that these communications provide a ready decompressive mechanism in cases of raised pulmonary artery pressure, and state that "no longer can the bronchial and pulmonary circulations be regarded as closed circuits. They communicate freely with each other on both the arterial and venous sides." Liebow (38) notes the work done by Marchand et al. and, on the basis of similar injection experiments of his own into diseased lungs, suggests that in failure of the right heart, where systemic venous pressure exceeds pulmonary pressure, a significant shunting of blood from right to left occurs.

Giant capillaries of the pleura

Von Hayek (62) coined the term "giant capillaries" in 1942 for the very broad subpleural capillaries which are about ten times wider than the alveolar capillaries. He differentiates these from AVA on the basis of their wall structure. Commenting on their large size, he says, "Indeed, I even find that the colored rubber masses injected through the pulmonary artery and vein meet in such capillaries." Presumably, then, these are in direct connection with the lesser circulation, and increased pulmonary artery pressure would not have to be present to give access to embolus passage.

DISCUSSION

The clinical syndromes produced by "pure" gas and fat embolism can be seen to have much in common, and both resemble severe dysbarism in many respects. In all, multiple sites of tissue ischemia in vital systems appear to cause the symptomatology. Presumably, this is caused, at least in part, by mechanical obstruction of small vessels by emboli. It is not the intent of this review to discuss the relative importance of gas and fat emboli in decompression sickness, or even to state that both are present in this disease. Pfrommer (46) states, "Today, we may say that the symptoms of decompression sickness result from the evolution of gaseous nitrogen, and possibly of other body gases, during environmental atmospheric pressure changes. The symptoms are the effects of the gases' influence, in some incompletely understood manner, on adjacent or distant vascular and somatic tissue. It is speculative to say more than this."

Emphasis should be placed on the ease with which microemboli can circulate. There is now sufficient evidence to assume that the AVA are plentiful in most, if not all, organs, allowing repeated recirculation of emboli. The question is now one of size and blood flow through these vessels; most authors agree that the AVA will

permit passage of particles (therefore emboli) of at least 20 to 30 μ . Coalescence of the emboli in areas of stasis accounts for blockage of larger vessels.

Likewise, in the healthy lung, the giant capillaries can account for passage of large number of emboli; and Von Hayek's work indicates AVA in addition to these. Furthermore, Bostroem and Piiper's work (11) in correlating gas exchange with passage of beads gives evidence that at least some emboli pass through functioning alveolar vessels. Rait (50) suggests that the lucid interval in some cases of decompression sickness can be attributed to the time taken for pulmonary edema to develop as a consequence of pulmonary capillary obstruction by emboli; pressures in pulmonary artery and right heart pressure then rise, allowing transcardiac transfer of emboli through a previously nonfunctioning foramen ovale. He also mentions the AVA as an alternate route in which a foramen ovale is not necessary. However, this explanation requires the presence of pulmonary edema prior to cerebral symptoms. The work of Peltier et al. (44) on serum lipase as in fat embolism suggests an alternate hypothesis. Perhaps hydrolysis of emboli with resultant vascular damage allows the emboli to pass the pulmonary circulation in large numbers, with the lucid interval being the time taken for vascular changes to occur. Whitteridge (66) has written a comprehensive review of the physiologic effects of multiple embolism to the lung, including mechanisms responsible for the respiratory and vascular changes.

If sufficient blockage of the pulmonary capillaries occurs, with attendant increased pulmonary artery and right heart pressure, the mechanisms of bronchopulmonary vascular shunting also must be considered. This mechanism in the production of generalized embolism deserves wider consideration; it would explain the latent period seen in air embolism (10) which the serum lipase explanation would not. Haymaker (27) includes this in his composite proposal for the etiology of decompression sickness.

The vertebral venous plexus deserves more attention as a route for the circulation of emboli; like the AVA, this system functions in the normal person, and no other transport mechanism or pathologic change need be invoked to produce cerebral symptoms.

Because of the widespread effect of emboli on major systems and because exact etiologic mechanisms cannot yet be defined, treatment of these syndromes remains largely symptomatic (39). Until the pathogenesis is clearly established, proper methods of treatment cannot be delineated. Adler (2) states, "It is one thing to treat vasoconstriction [referring to the vasospasm theory] and another to combat vasodilation [referring to the shock and vascular atonia theory]." More progress has been made in prevention than in diagnosis and treatment. Prevention of embolus formation is one example: considerable progress has been made in the prevention of dysbarism by means of protective garments, denitrogenation, and the like. Prevention of "pure" fat embolism, at present, is synonymous with prevention of trauma; in this area, further studies on the importance of lipemia, and reduction of serum lipids, are indicated. Extracorporeal circulation could be utilized in the estimation of relative importance of the various circulatory pathways by which emboli are circulated. For instance, the pulmonary circulation could be bypassed to estimate efficiency of the lungs as a filter. This technic is now being used in studies of the role of gas emboli in dysbarism, in the Physiology Department of the USAF School of Aerospace Medicine (35). Dysbarism studies which might be of assistance in outlining specific etiology, in addition to those mentioned above, are:

1. Analysis of the circulating blood for fat and gas emboli, in experimental animal during decompression. This would include autopsies performed at the reduced pressures where symptoms occurred.
2. Examination of experimental animals for fat emboli after decompression followed by overcompression (to eliminate gas emboli).
3. Development of delayed neurocirculatory collapse in animals, perhaps by varying the amounts of decompression and lipemia.

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