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Pathophysiology and Clinical Implications

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Gas embolism is a known complication of various invasive procedures, and its management is well established. The consequence of gas microemboli, microbubbles, is underrecognized and usually overlooked in daily practice. We present the current data regarding the pathophysiology of microemboli and their clinical consequences. Microbubbles originate mainly in extracorporeal lines and devices, such as cardiopulmonary bypass and dialysis machines, but may be endogenous in cases of decompression sickness or mechanical heart valves. Circulating in the blood stream, microbubbles lodge in the capillary bed of various organs, mainly the lungs. The microbubble obstructs blood flow in the capillary, thus causing tissue ischemia, followed by inflammatory response and complement activation. Aggregation of platelets and clot formation occurs as well, leading to further obstruction of microcirculation and tissue damage. In this review, we present evidence of the biological and clinical detrimental effects of microbubbles as demonstrated by studies in animal models and humans, and discuss management of the microbubble problem with regard to detection, prevention, and treatment. ***(CHEST 2005; 128:2918–2932)***

Key words: dialysis; lung; pulmonary hypertension; surgery

Abbreviations: DCS = decompression sickness; HBO = hyperbaric oxygen; PMN = polymorphonuclear leukocyte

> The earth has bubbles, as the water has, and, these are of them. Whither are they vanished?
>
> Banquo
>
> Into the air; and what seem'd corporal melted as breath into the wind. . . "
>
> Macbeth, Act I, Scene III William Shakespeare

The rapid advancement of technology in the past few decades has brought new areas to medical practice. One recent development is the detection of microbubbles by ultrasound. Using this updated technique, clinicians and researchers have found that the phenomenon of microbubbles is widespread. Microbubbles originate mainly in extracorporeal lines and devices, such as cardiopulmonary bypass and dialysis machines, but may be endogenous in cases of decompression sickness or mechanical heart valves. Circulating in the blood stream, microbubbles lodge in the capillary bed of various organs, causing local reactions. Our natural tendency is to overlook minute particles, some of which are invisible, believing them to be harmless. However, solid data show that microbubbles are of clinical importance. In this review, we present evidence of the biological and clinical effects of microbubbles, as demonstrated by studies in animal models and humans, and discuss the management of the microbubble problem with regard to detection, prevention, and treatment.

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Definition

Gas embolism is an iatrogenic event in which gas enters the circulation and can result in serious morbidity and death.[1] Animal studies[2,3] have shown that rapid infusion of a large volume of air may be fatal. Our knowledge of the consequences of small-quantity air emboli is lacking. The cutoff point between the occurrence of a major catastrophic episode and subtle but unequivocally important symptoms is yet undefined. An arbitrary definition of microbubble size may be erroneous since only a bubble of a diameter smaller than the capillary can travel through the circulatory system without leaving an imprint and be accepted as safe.[4] Furthermore, in the biological setting, there is a dynamic, constant process of small bubbles fusing to create large bubbles, and large bubbles splitting into many small ones; thus, a few "harmless" microbubbles could coalesce into one injurious large bubble.

The composition of a gas bubble is usually air or

oxygen, although the medical use of carbon dioxide, nitrous oxide, and nitrogen can also result in gas emboli.[5–7] Gas composition affects bubble elimination time in the body, since each gas has its own solubility coefficient and diffusion coefficient in a given fluid.[8] It is reasonable to believe that gas composition also affects local tissue reaction and systemic response, although research on this subject is limited.[9]

Gas bubbles usually originate in extracorporeal tubing, infusing with the fluids into the blood stream. The bubbles may be present while priming and preparing the lines for use, or newly formed as a result of turbulent flow in the tubing and at the vascular access. Differences in temperature is another possible cause for bubble generation in lines, since warming initiates bubble formation, such as when an active blood warming system is used.[10] The course of the bubble in an extracorporeal infusion set is affected by many factors, principally two opposing forces: firstly, the buoyant force of a bubble, which takes it upward in a standard drip chamber; and, secondly, the driving force of the fluid flow, by which the bubble is carried into the patient's body. For illustration purposes, assuming a flow rate of $8.33 \cdot 10^{-6}$ m^3 s^{-1} (500 mL/min^{-1}) [flow rate of a rapid infusion system], these forces are equal to a $441 \cdot 0^{-6}$ m (441 μm) diameter air bubble in the blood, which means that a smaller bubble will be carried into the patient's blood stream and a larger bubble will remain in the drip chamber.

Microbubbles may be created *de novo* in a patient without connection to the extracorporeal system. One example is the decompression sickness (DCS) of divers, and another is the mechanical prosthetic heart valve, generating microbubbles that are demonstrated *in vivo*.[11–13] Both conditions will be discussed later in this review. There is a spectrum of scenarios in which the extremes are a single exposure to very high volumes in contrast to recurrent chronic exposure to small volumes of microbubbles. The clinical implications of the microbubble phenomenon depends on the extent and cumulative effect of such an event.[14]

Dynamics of Microbubble Elimination

The fundamentals for the dissolvance of a gas bubble in a solution have been formulated by Epstein and Plesset.[15] The formula takes into account several parameters, including the gas-liquid diffusion constant, universal gas constant, saturation concentration of the given gas, temperature, surface tension, ambient pressure, and the radius of the bubble (Appendix). When using the equation for elimination of air microbubbles in the bloodstream, some of these parameters can be regarded as constants since, in most clinical settings, changes in temperature, ambient pressure, and gas composition (almost always air) are negligible.[16] An exception is the cardiopulmonary bypass procedure, in which body temperature is significantly lowered.[17] Alterations in the physiologic steady state can also be detected in DCS, where ambient pressure rapidly decreases on returning to the water surface,[18] and in the hyperbaric chamber, where ambient pressure is high.[19]

Bubble dissolvance occurs when the surface tension sets off diffusion of the gas to the surrounding liquid phase as it generates an overpressure inside the bubble.[20] According to the Epstein-Plesset equation, dissolution times for an air bubble in water are 1 s for a 10^{-6} m^3 (1 μm) radius bubble, 1 to 6 s for 10^{-5} m (10 μm), 100 to 600 s for 10^{-4} m (100 μm), and 1 to 6 million s (11 to 70 days!) for 10^{-3} m (1 mm) bubble. It is important to note that these numbers refer to a spherical bubble in water. In the human body, the shape of the bubble changes during its journey in the circulation, becoming more elongated and slender as it floats further into the periphery. As the bubble is entrapped in the vessel, it is remodeled into a cylinder with hemispherical end cups.[21] In a typical entrapped bubble, the length of the cylindrical bubble is greater than its radius. Therefore, the dissolution time is increased by at least 50% compared to the calculated absorption time for a spherical bubble with the same initial volume.[21] Regarding the liquid composition, a layer of denaturated proteins has been seen at the bubble-blood interface,[21,22] further slowing down the bubble disappearance process *in vivo*. When the gas composition is not air, bubble elimination time may be changed as well.[21,23,24] It could be concluded that the theoretical model derived from the Epstein-Plesset equation underestimates the actual life span of a gas bubble in the body, hence its possible harmful effects.

There have been studies[25,26] that demonstrate the beneficial effect of surfactant on bubble elimination. It seems that by changing the bubble surface tension, a surfactant promotes bubble absorption. It also reduces bubble adhesion forces and, in this way, protects the endothelium from additional injury.[27] The beneficial effect of surfactants has been demonstrated *in vitro*, although it has not been tried in humans for microbubble elimination.

Mechanisms of Microbubble Tissue Damage

The immediate and more rapid event following microbubble injection is the obstruction of blood

flow in the capillary distal and proximal to the occluding particle. This causes antegrade and retrograde tissue ischemia along with changes of pressures in the circulation and interstitium around the affected blood vessel. Instantaneously, the inflammatory response and complement activation takes place since the body reacts toward the bubble as a foreign substance (Table 1). We discuss each of these processes separately in the following chapters, although these events are inseparable in the biological situation. Nearly all research regarding microbubble-induced tissue damage was done in lung models, since the lung is the main organ exposed to venous emboli.

Mechanical Tissue Damage

The microbubble travels in the blood stream until it is lodged in the microcirculation. During its course, the bubble is compressed against the endothelial capillary wall, causing functional stripping of endothelial cells and an increase of large-pore radii.[28] In addition, gaps between endothelial cells are created both in pulmonary and bronchial microvessels following air embolism.[29] Normally, endothelial cells are tightly joined, preventing intravascular fluids from pouring out into the surrounding tissue. Gap formation allows leakage and resultant interstitial edema. The hydrostatic pressure upstream to the bubble increases, causing further fluid passage into the interstitium. Studies[30,31] using an animal model of air emboli in the sheep lung found sustained elevation in pulmonary artery pressure and pulmonary vascular resistance. Repeated episodes of air embolism have been shown to cause an increase in thickness of the muscular pulmonary arteries and some structural changes of pulmonary hypertension.[32–34] Downstream to the obstructing bubble, tissue ischemia takes place depending on its sensitivity to hypoxic conditions. The endothelium may be protected by surfactant, as was established by Suzuki and colleagues.[27] In their study on microvessel preparation injected with microbubbles, surfactant reduced the bubble adhesion force and preserved basic endothelial structure and vasodilatory function.

Inflammatory Response

Our understanding of microbubble-induced inflammatory response originates from early studies[35,36] of pulmonary edema in animal models. Neutrophils play a central role in mediating air embolism-induced lung injury. They aggregate around the bubble to produce clumps. A local destructive process takes place, probably by superoxide and hydroxyl radical production and proteolytic enzyme release. These molecules increase membrane permeability to fluids and proteins and facilitate interstitial pulmonary edema.[30] A study[37] of leukopenic animals showed that leukocyte depletion attenuated the increased microvascular permeability that follows venous air embolization. The pathophysiologic process is independent of bubble composition and starts as the circulating bubble is trapped in a small arteriole (diameter 10^{-4} to 10^{-3} m) [100 to 1,000 μm] or in a capillary.[38] Although evidence for the inflammatory response to microbubbles is solid, our understanding of the pathophysiologic process is incomplete and awaits further investigation.

The Complement

Activation of complement by circulating microbubbles commences at the air-liquid interface that surrounds gas-filled particle.[39,40] Ward et al[41] demonstrated that prior depletion of complement proteins with a cobra venom factor reduced the occurrence of complement activation and lowered the incidence of decompression sickness in rabbits. In humans, Stevens et al[42] reported that increased levels of activated plasma proteins, C3a and C5a, correlated with the occurrence of DCS after saturation diving. C3a and C5a trigger polymorphonuclear leukocytes (PMNs) and stimulate mast cells to release histamine, which increases vascular permeability. Activated PMNs further augment tissue damage by releasing cytotoxic substances, such as active oxygen metabolites and arachidonic acid products.[43,44] PMN-derived oxygen metabolites cause lipid peroxidation in endothelial cell membranes. The arachidonic acid products such as prostaglandins

Table 1—*Mechanisms of Microbubble Tissue Damage*

Mechanical	Inflammatory Response	Complement	Clotting Activation
Compression against vessel wall	Neutrophils sequestration around bubble	Increased levels of C3a and C5a	Platelet aggregation
Gap formation	Increased permeability	Triggering PMNs	Thrombin production
Fluid leakage	Radical species production	Histamine release	Thrombus generation
Muscular hypertrophy	Clot deposition	Radical species production	
		Prostaglandin, leukotriene synthesis	

and leukotrienes are vasoactive factors, and all alter microvascular permeability. In order to attenuate the complement-mediated endothelial damage resulting from gaseous microemboli, Nossum et al[45] used anti-C5a monoclonal antibodies preparation. They showed reduced PMN infiltration in pretreated rabbits compared with the control group and concluded that anti-C5a protects the endothelium against injury caused by small amounts of gas bubbles. It is therefore concluded that complement activation is involved in microbubble-induced tissue damage.

The Clotting System

Microbubbles affect clotting through both activating coagulation and inducing platelet aggregation. The result is clot formation at the bubble proximity. Later, fibrinolysis and local reaction to the thrombus occurs. The bubble surface acts as a foreign substance and activates the coagulation cascade.[46] Microbubble gas-blood interface adsorbs macromolecules that are normally present in the blood. The adsorption provokes molecular conformational changes, such as unfolding, and exposes regions of proteins that trigger blood coagulation.[22] Using thrombin production assay, sparging (microbubble embolization) increases thrombin production 2.1- to 3.7-fold compared with bubble-free blood.[47] The addition of surfactants to the coagulation assay attenuated thrombin production in sparged samples by 30 to 70%, probably due to occupancy of the gas-blood interface.

Early studies[48,49] have shown that platelets adhere to the bubble surfaces, where the bubbles act as platelet agonists with respect to aggregation. Additionally, microbubble-induced endothelial damage causes tissue factor expression and subsequent platelet activation and thrombus generation.[49,50] Platelets accumulation around air bubbles in the blood occurs due to cellular reaction, but also as a result of the physicochemical flotation process, as Ritz-Timme et al[51] demonstrated. In their study, attachment of particles (cells) to flowing air bubbles in an aqueous medium (blood) was demonstrated. By plugging blood vessels, the thrombus causes hypoxic local damage.[52] Indeed, prophylactic heparinization had been shown to reduce neurologic impairment after cerebral arterial air embolism in the rabbit,[53] verifying that some of the damage is due to thromboinflammatory responses at sites of air-injured endothelium. Another direction may be preventing platelet accumulation using antiplatelet drugs. Moon et al[54] proposed that antiplatelet drugs, combined with other pharmacologic agents, may be useful adjuncts to recompression therapy in cases of decompression sickness and iatrogenic gas embolism, although this treatment "requires further study."

Clinical Consequences of Circulating Microbubbles

The clinical outcome of air embolism depends on the size of the bubble, location (organ/tissue), general status, and comorbidity of the patient, plus many known and unknown factors.[55] Large air embolism is usually disastrous, both in the venous and arterial circulation.[56–58] The natural course of a large venous embolism is migration into the pulmonary circulation and obstruction of the right ventricular outflow, acute increased resistance to the right ventricle and diminished left ventricular preload, followed by cardiovascular collapse.[1,59] Air emboli in arterial vessels cause symptoms of end-artery obstruction and tissue ischemia and necrosis. Although arterial air emboli could reach any organ, occlusion of cerebral and cardiac circulation is particularly deleterious because these systems are highly vulnerable to hypoxia and go through irreversible cellular damage. The result of such an event may be massive brain ischemia and stroke or myocardial ischemia and infarction. Both could be fatal. The detection of such catastrophic events and resuscitative measurements are well known.[1,60,61] Less is known about the results of small air emboli in the venous or arterial circulation. A small quantity of microbubbles may be clinically silent, while recurrent exposure to microbubbles causes a slow smoldering chronic effect that is difficult to detect but has important consequences.

The patient's comorbidity may also influence the outcome of circulating air emboli. When there is a right-to-left shunt, venous air emboli may traverse to the arterial circulation and cause organ ischemia. Such a course of events is termed *paradoxical air embolism*,[62] and there are a few mechanisms by which it may occur. One is passage of gas through a cardiac right-to-left shunt into the systemic circulation. The prevalence of a cardiac right-to-left shunt ranges between 15 to 40% in various studies,[63,64] usually as a result of patent foramen ovale but may be caused by other cardiac anatomic anomalies. Neonates are vulnerable to developing arterialization of venous air since the foramen ovale may remain patent for some time after birth.[65] A right-to-left shunt might also be extra-cardiac, mostly from dilatation of pulmonary vessels, causing an intrapulmonary shunt in ARDS. In many cases the existence of such a shunt is unknown to the patient or physician, and the risk of paradoxical emboli is not taken into account. The passage of air emboli from the venous to the arterial circulation occurs also when the

volume of air is vast. The pulmonary circulation filtration capability had been studied by Butler and colleagues[3,66,67] in animal models. They found that when a volume of venous air emboli was $> 3.5 \cdot 10^{-7}$ m^3 kg^{-1} (0.35 mL kg^{-1}) the filtration threshold was exceeded, leading to arterial spillover of bubbles in 50% of the animals, and increased to 71% for an air dose of $4 \cdot 10^{-7}$ m^3 kg^{-1} (0.40 mL kg^{-1}). These studies draw attention to the possibility of each venous air embolism turning into an arterial one, depending on gas volume and injection time. The lung itself is injured by performing the nonrespiratory function of filtering the venous blood, while protecting the arterial system from microemboli. Researchers have simulated microembolic conditions in animal models in order to examine the resultant changes in the lungs. Various models have been used. One model applied starch microemboli (diameter [63 to 74] $\cdot 10^{-6}$ m [63 to 74 μm]) to investigate blood gas alterations following embolism.[68–70] In another animal model, glass beads (diameter [1 to 5]) $\cdot 10^{-4}$ m [100 to 500 μm]) were injected into lambs[37,71,72] or dogs.[28] A model of air emboli was used as well.[30–32] All studies clearly demonstrated that pulmonary edema is the end point of venous embolism and, when repeated, the structural pathologic changes in the lung resemble those seen in pulmonary hypertension.[33,34]

Scientific evidence from humans is limited; nevertheless, it supports most of the laboratory findings. The inflammatory response following pulmonary microemboli has been reported in a few cases.[73,74] CT scan and pulmonary function tests demonstrated the effect of pulmonary emboli on the lung to cause air trapping and mosaic perfusion.[75,76] These publications refer to cases of macroscopic pulmonary emboli and not microbubble events. Investigations on human lungs following microbubble injury are found mainly in the diving medicine literature and are discussed below.

Procedures and Events Generating Microbubbles

Almost every invasive procedure may cause the introduction of microbubbles into the blood stream.[77] Of course, the more invasive and interventional the procedure, the greater is the risk of microbubble generation. There have been an increasing number of reports[78,79] about air microemboli in some procedures, such as cerebral angiography and left-heart catheterization. Admittedly, most microembolic events are silent,[80] but some are symptomatic and the phenomenon cannot be ignored. We concentrated on procedures in which the bubble load is high and affect critical organs, including the brain and the lung (Table 2).

Cardiopulmonary Bypass

Major and minor CNS complications following open-heart surgery are frequent difficult clinical problems.[81–84] The American College of Cardiology/American Heart Association guidelines[85] have classified postoperative neurologic deficits into two types. Type 1 deficits include a major focal neurologic deficit, stupor or coma. Type 2 deficits are deterioration of intellectual function, confusion, memory deficits, agitation, or seizures without evidence of focal injury. The incidence of cerebral complications after cardiac surgery varies widely according to age, sex, type of procedure, atherosclerotic disease of the aorta, and other factors.[86,87] Stroke, for example, ranges from 5% in patients after coronary artery bypass graft surgery to almost 9% in patients > 75 years of age who undergo the same operation, and up to nearly 16% in patients following valve surgery.[82,86] The incidence of apparent cognitive damage, such as deterioration of memory, may reach 60% 1 week after open-heart surgery, falling to 25 to 30% from 2 months to 1 year postoperatively.[88] The incidence of cognitive dysfunction at 1 week following cardiac surgery is approximately twice that of noncardiac surgery.[89] In addition to patient morbidity, adverse cerebral outcome is associated with increased mortality, prolonged hospitalization, and excessive use of intermediate or long-term care facilities.[81,90] Roach and colleagues[81] calculated the additional cost of in-hospital neurologic morbidity after cardiac surgery as approximately $400 million annually. They estimated that true costs, including long-term out-of-hospital medical and rehabilitative services, probably result in additional expenditures ranging from 5 to 10 times narrow in-hospital costs, or $2 to $4 billion annually.[81]

There are several factors that contribute to the adverse neurologic outcome after open-heart surgery, such as reduced cerebral blood flow, local or systemic inflammatory response, cellular edema, and the effect of anesthetic drugs. These factors along

Table 2—*Sources of Microbubbles*

Procedures generating microbubbles
Cardiopulmonary bypass
Hemodialysis
High-flow lines
Others, invasive procedures.
Endogenous sources of microbubbles
Mechanical heart valves
DCS

with gas and solid emboli from the cardiopulmonary bypass set and from endovascular origin produce cumulative effects on brain function during and after surgery.[83,17] Cardiopulmonary bypass machines are used in most open-heart surgeries to oxygenate and pump the blood while the heart is arrested. Solid or gas emboli from various sources in the extracorporeal set and tubes may drift into the aorta and systemic circulation.[91,92] To minimize embolization, a screen filter is installed on the arterial line that returns blood to the aorta. The filter pores are 28 to $40 \cdot 10^{-6}$ m (28 to 40 μm), allowing smaller emboli to pass through. Nevertheless, larger air and fat emboli also pass through and enter the circulation downstream to the filter whenever their load is high.[89,17] Microbubbles that traverse the filter join and become large bubbles. Air, atherosclerotic debris, and fat microemboli that enter the systemic circulation and arrive at the brain cause neuronal necrosis by blocking small cerebral vessels.[93] It has been established that postoperative adverse neurologic deficit correlates positively with numbers of emboli to which the patient is exposed during surgery.[94–96]

Several methods have been suggested, aimed at reducing the risk of neurologic complications following open-heart surgery. One of the main strategies to avoid brain injury is reducing emboli load during surgery.[97–99] Other means to improve the neurologic outcome include modification of surgical techniques[100,101] and the use of neuroprotective anesthetic techniques and drugs to enhance cerebral oxygenation and decrease cellular metabolism.[102–104] None of the above measures resulted in complete brain protection, but practicing a few together may be beneficial. Further protective means are warranted to improve outcome in the clinical scene.

Hemodialysis

As far back as 1975, there was evidence of pulmonary microembolization during hemodialysis.[105] The subject of dialysis-induced microemboli has been revisited, mainly as a consequence of better detection technology, raising major concerns as to whether their presence can be overlooked or if practical means of emboli elimination must be developed. In 2000, Woltmann et al[106] used B-mode and spectral mode ultrasound to detect microemboli occurring in the hemodialysis access of two patients. The authors postulated that these microemboli developed from turbulent blood flow around the venous access. A prospective study[107] of 25 patients published that year showed microemboli in the subclavian vein (downstream from the arteriovenous fistula); the authors concluded that gas microemboli are formed by the blood pump of the hemodialysis machine. In 2002, Droste and colleagues[108] used pulsed-Doppler ultrasound to demonstrate a continuous shower of microemboli into the pulmonary vasculature during dialysis and hypothesized that this may explain the high pulmonary morbidity in long-term dialysis patients. Those microemboli are most probably gaseous, as suggested by the ultrasound high relative intensity signal. The origin of these microbubbles may be in air bubbles already in the hemodialysis tubes and filter before the procedure, or entering the blood stream during connection and disconnection of the lines, or formation of gas bubbles as the result of pressure gradients and turbulent flow in the tubes and access. In a follow-up study,[109] a significant reduction of microembolization was found when prefilled instead of dry dialyzers were used. The majority of these studies imply that the composition of microemboli detected during dialysis is gas.

Today, hemodialysis devices are equipped with ultrasonic detectors of air larger than $850 \cdot 10^{-6}$ m (850 μm) and alarms that announce the occurrence of an extremely large air bubble event. Smaller emboli, however, even in large numbers, do not activate the alarm. In the past, two cases of dialysis equipment recall were enforced by the US Food and Drug Administration. In the first, in 1992, approximately 4,000 devices were rejected due to failure of the ultrasonic bubble system, which resulted in air observed in the venous line that reached the patients.[110] The second US Food and Drug Administration recall included approximately 3,000 hemodialysis devices in which air bubbles were detected in the extracorporeal system.[111] These cases illustrate the shortcomings of current ultrasonic bubble detectors, which are set to discover relatively large bubbles but allow the entrance of smaller but significant microbubbles.

The patient with end-stage renal failure undergoes approximately three sessions of hemodialysis a week, 150 sessions yearly. Each session takes a few hours, in which the patient is exposed to a microbubble shower. Microbubbles originate from the dialysis tubes or filter flow in the venous vasculature and are trapped in the pulmonary circulation. Thus, the hemodialysis patient may suffer both acute and chronic lung injury due to a microbubble shower. Regarding the acute effect, the main clinical indication for respiratory insult is hypoxemia, which is a well-known symptom during hemodialysis.[112] Several theories have been suggested to explain this event, such as hypoventilation due to changes of pH, direct effect of acetate on the central respiratory center, and increased alveolar-arterial oxygen gradient due to complement activation.[113] Nevertheless,

the damage caused by exposure to loads of microbubbles should not be overlooked in explaining acute hypoxemia during hemodialysis. Chronically, the recurrent ongoing microbubble lung injury may explain the high pulmonary morbidity, manifested as increased pulmonary artery pressure, of long-term dialysis patients,[114,115] and is "a mimic of pulmonary thromboembolism."[116] It has been established that > 30% of hemodialysis, but not peritoneal dialysis, patients had pulmonary hypertension that normalized when kidney transplantation was performed.[117,118] The occurrence of pulmonary hypertension as a result of recurrent events of air emboli was demonstrated decades ago in animal models.[33,34] Studies in hemodialysis patients focusing on the connection between microbubble load and development of pulmonary hypertension are warranted.

The damage caused by microbubbles may be more detrimental in case of cardiac or extracardiac right-to-left shunt, which may be found in up to 40% of the population.[64] In those cases, air emboli may enter the cerebral circulation and cause varying degrees of neurologic damage.[119] Indeed, the above-noted clinical studies[106–109] that described microemboli during dialysis had either no patient with a shunt[108,109] or did not report that detail in the study.[106,107] Nevertheless, it is reasonable to believe that a patient with a right-to-left shunt is at higher risk for neurologic morbidity as a result of venous air embolism during hemodialysis. Cerebral atrophy and deterioration of neurocognitive functions in chronic hemodialysis patients is a recognized problem that correlates with the duration of dialysis treatment.[120–122] Various factors may promote cerebral atrophy in these patients, such as uremic neuropathy, aluminum intoxication, impaired cerebral circulation, and hypertension. The additional risk of cerebral damage due to microbubbles has not been investigated yet.

High-Flow Lines

The use of high-flow lines is prevalent in almost every operating room where major surgery is performed, in ICUs, emergency shock-trauma departments, and whenever massive blood loss is predicted.[123,124] Most current devices use large-bore, low-resistance fluid sets that enable the administration of a large volume and, at the same time, warming the infused solution or blood. The devices are equipped with an "air eliminator" designed to vent air from the line before entering the patient. Nevertheless, these eliminators are ineffective when large volumes are administered[125,126] and in eliminating microbubbles. The air in the system originates from three sources: it may be in the line before its priming and flushed in with the fluids; it may come from newly formed bubbles caused by turbulent flow (the amount of air detected in high flow lines correlates with flow rates[10]); and, finally, as one of the manufacturers of these devices warns, microbubbles are released from the fluid as it is warmed.[127] These microbubbles are formed continuously within the system and present a constant source of air. It is hard to evaluate the damage caused to the patient from microbubble exposure. In the scenario of massive bleeding and an unstable patient, the physician who resuscitates the patient cannot pay attention to each air bubble. Furthermore, some of these bubbles are small and, in the viscous transfused blood, are practically invisible. Therefore, new and effective air eliminators are needed to improve our detection and prevention of microbubbles in high flow systems.

Mechanical Heart Valves

In the early 1990s, a phenomenon of spontaneous endogenous ultrasound signals was reported in patients with a mechanical mitral valve.[128] The echocardiographic signal was described as bright and of high velocity; it appeared during systole and was regarded at first as an artifact. Later, improvement of ultrasound technology led researchers to recognize that the echocardiographic signal represented microbubbles formed due to local high-pressure gradients at the level of the valve leaflets, a process known as cavitation.[129] Kaps et al[130] succeeded in reducing echocardiographic signals in patients with mechanical heart valves by breathing 100% oxygen under hyperbaric conditions, proving that these microemboli were gaseous and not solid. Deklunder et al[13,131,132] used transcranial Doppler echocardiography in patients with prosthetic mechanical and biological heart valves with neurologic symptoms. They found that high-intensity transient signals were frequently found in the cerebral arteries of patients with mechanical heart valves. They attributed these signals to microbubbles formed by cavitation. Furthermore, they assumed that cognitive impairments may occur in these patients due to persistent microbubble generation by the valve, and confirmed this hypothesis by showing a significant decrease in working memory performance in patients with mechanical heart valves compared with biological valves and control subjects. Girod et al[133] suggested another explanation for microbubble formation by the mechanical valve. In their *in vitro* study,[133] they measured the dimensions of the bubbles and the time of their appearance. They concluded that microbubbles are the result of degassing of CO_2 in blood rather than the cavitation effect, since cavitation is a physical phenomenon of short duration whereas bubble formation by a mechanical heart

valve is a much longer generation period, matching the degassing hypothesis. The finding of microbubble formation drives intensive engineering efforts to construct the optimal valve design that will be devoid of gas microembolization.[14,134]

Diving and DCS

The four main pathologies in diving medicine are barotraumas (cranial sinuses, otic and pulmonary), DCS, pulmonary edema, and toxic effect of increased partial pressure of gases.[135] The pathophysiology related to diving morbidity and mortality results from gas behavior during altering pressures. Similarly, aviation medicine and some of the extreme-sport types, such as air diving, contend with the same health problems due to intense changes in ambient pressure.

According to Boyle's law, in constant temperature the pressure (P) varies inversely as volume (V): $P_1V_1 = P_2V_2$. Thus, for every 10 m of depth diving, the pressure increases one atmosphere and air volume decreases 50%. The opposite happens on returning to the surface. Acute changes of pressure affect mainly organs and cavities that contain gas. As the pressure decreases, the gas volume expands and may rupture the surrounding membranes, causing barotrauma.

Another physical gas law is the Henry law, which states that the amount of a given gas dissolved in a liquid at a constant temperature is directly proportional to the partial pressure of that gas. Accordingly, when a diver breathes air in high pressure, air from the lungs is dissolved in body fluids and blood and is transported to peripheral organs. Oxygen is used for tissue metabolism, while nitrogen, which is physiologically inert, is not.[136] As the diver returns to surface level, the gas saturation in the fluid decreases and nitrogen bubbles are formed in all tissues causing DCS. This process depends on the rate of change in pressures and is termed DCS. The US Navy and the Royal Navy have decompression tables, instructing the use of stops in returning to the surface and enabling body adjustment to changes in pressure, thus reducing the risk of DCS. Nevertheless, severe DCS has been described within safe table limits.[137] Early studies[138,139] detected bubbles in the circulation of asymptomatic divers during decompression. These findings indicate that bubble formation may be clinically silent to some degree or amount of bubbles. DCS is an accurate example of humans exposed to microbubbles in the circulation, and thus can demonstrate the clinical presentation of that event. It is customary to classify DCS into two types based on the severity of symptoms.[136] Type 1 DCS is milder, expressed by joint pain, pruritus, and skin rash. More severe symptoms are seen in type 2 DCS. These are neurologic symptoms such as headache, blurred vision, parenthesis, paraparesis and, in serious cases, convulsions and death. The neurologic manifestations are attributed to bubble embolization in the CNS. Again, clinical studies[140,141] suggest that subclinical cerebral damage occurs in divers, raising the possibility that microbubble damage is underdiagnosed due to difficulties in detection and not because they are not present. The effect of recurrent diving was described by Skogstad et al,[142] who conducted a study of lung function in professional divers and found that exposure to diving contributed to changes in pulmonary function, mostly affecting small airway conductance. The authors interpreted these changes as thickening of bronchiole walls and loss of lung elasticity.

The effect of recurrent diving on brain function has been studied over the years, using various tests. EEG, CT, and MRI were used, as well as neuropsychologic tests. Although most researchers[143–146] found pathologic alterations comparing professional and recreational divers to control subjects, contradictory results have been published as well.[147] Most authors,[143,145,146] however, agree that the prevalence of changes in divers is inversely related to diving depth, cumulative diving time, participation in "unsafe diving," and DCS. The pathophysiology of the cumulative effect of recurrent diving is not yet fully understood and may be the basis for comprehension microbubble injury.

Detection and Prevention of Microbubble Exposure

Detection

Attempting to prevent the threat of air embolism during a cardiopulmonary bypass machine event, numerous devices were designed. In 1980, an air embolism detection device (Air-Bubble Detector System; Sarns; Ann Arbor, MI) was presented as a tool capable of detecting the presence of macroscopic air emboli (10^{-6} m^3 [1 mL] or larger) using an infrared light source and a photocell receptor.[148] When the detector was turned on, a control unit caused the cardiopulmonary bypass pump to shut off. A few false alarms triggered the pump shutoff, such as electrocauterization, defibrillation of the patient, high-pitched sounds, and low hematocrit, which made the detector difficult to operate.[148] The use of ultrasound technology for detecting air bubbles was studied first on an animal model.[149] Pulsed-Doppler ultrasound detected microbubbles within a fluid line[150] and *in vivo*.[151] The continuous progress of technology improved equipment and

facilitated better detection capabilities.[152,153] Transcranial Doppler ultrasound made it possible to detect microbubbles in the cerebral circulation of patients during surgery, enabling the study of the effect of various types of oxygenators or atrial fibrillation on microbubble showering in real time.[154–157] The main disadvantage of transcranial Doppler ultrasound is the fact that bubbles are seen in the circulation postfactum, without the capability of preventing the event. Another recently presented technique to detect bubbles uses a tetrapolar electrical impedance measurement.[158] Tested *in vitro*, this noninvasive device detected 10^{-3} m (0.5 mm) diameter bubbles at a depth of $5.3 \cdot 10^{-3}$ m (5.3 mm). However, this device is not sensitive enough to deal with microbubbles. Therefore, in medical procedures prone to microbubble generation, the only current aid is still Doppler ultrasound.

Filters

Knowing the possible clinical consequences of microbubble exposure, it is agreed that prevention is the best policy, which means eliminating air from fluids before they enter the body. There are several filters used for microbubble elimination. The most common is a filter that is installed on the line and functions as a dense net for bubbles, as in cardiopulmonary bypass machines (see above). The filter traps bubbles that are larger than its pores. There are a few disadvantages to the use of these filters. The add-on to the tubing increases resistance to flow, as indicated by a pressure drop through the filter.[159,160] Moreover, when filtering blood, after a short time of function, it is filled with debris and fibrin and the resistance increases even further. In severe cases, the used filter may completely block the flow within the line. In addition, chemicals within the filter activate coagulation cascade, the complement, the immune response, and other biological reactions to foreign materials. A third disadvantage is the hazard of the chemical composing the filter, which may be toxic, as happened in 2001 in Europe.[161] In that case, the deaths of more than 50 hemodialysis patients have been linked to the dialysis membrane. Investigators found the deaths were connected to a solvent chemical used in the manufacturing process not completely removed from the filters. The last disadvantage of filters in use today is their inability to eliminate all microbubbles from the system, as demonstrated in open-heart surgery.[17,89] The conclusion of these disadvantages is that the future optimal device for microbubble elimination should use technologies other than mechanical obstructing filtering devices. For example, a multipurpose ultrasonic bubble detector and neutralizer capable of filtering small microbubbles from the blood, was recently developed (Thera-Sonics Ultrasound Technologies; Jordan Valley, Israel). It uses an ultrasound field to push microbubbles through an acoustic transparent module where they can be collected and removed. The possibility of affecting microbubbles in the blood by ultrasound was already shown by Schwarz et al.[162] Another type of filter was evaluated by Schonburg et al,[163] who tested a dynamic bubble trap in which the bubbles are directed to the center of the blood flow and collected in its distal end, where they are returned to the reservoir. Schonburg et al[163] found a significant reduction of microbubbles in the arterial line while using the DBT.

Management

The treatment of large air emboli is well established.[1,60,61] Little is written about the management of microbubble injury. Some of the known therapeutic modalities employed for massive air embolism may be applied in the case of microbubbles. In both scenarios, prevention is the best approach as "an ounce of prevention is worth a pound of cure." When the event of air embolism, macro as well as micro, has occurred, early detection is required to facilitate immediate action to interrupt the cause. While the detection of large air emboli is easy, usually manifested by acute cardiovascular collapse or sudden overt deterioration of the neurocognitive or motor functions, catastrophic in nature, the presentation of a microbubble event is more subtle and difficult to detect. We chose not to specify the treatment of large air emboli, which require cardiopulmonary resuscitation (Muth and Shank[1] and Petts and Presson[61]) and focused on small air emboli (Table 3).

Hyperbaric oxygen (HBO) is a treatment modality that is applied in DCS of divers[54,164] and in cases of large air emboli occurring during various medical procedures. Several clinical studies[165–167] have been published, demonstrating improvement in neurologic outcome following HBO therapy, although no

Table 3—*Management of Microbubble Event*

Prevention
Drip chambers; filters
HBO
Drugs
Heparin
Barbiturates
Corticosteroids
Lidocaine
Perflurocarbons (?)
Surfactants (?)

prospective randomized trials have been conducted. HBO should be employed as soon as possible after the insult, although delayed treatment is also helpful.[168] A few physiologic modes of action can explain the beneficial outcome of HBO therapy. HBO reduces the volume of intravascular bubbles by enhancing the ambient pressure (see Appendix: Epstein-Plesset equation); the increase in oxygen partial pressure favors denitrogenation. Furthermore, HBO increases the partial pressure of dissolved oxygen in the blood, allowing better oxygenation of ischemic tissues.[59,169] The physical properties of HBO therapy are applicable in a microbubble event and, although no study has been published to confirm this hypothesis, it is reasonable to believe that such therapy could be helpful in symptomatic microbubble cases as well.

The use of drugs in air embolism is empirical and controversial.[54,59] Most studies examined cases of cerebral air emboli and followed the neurologic outcome. Several drugs were tested in patients with air emboli, especially for managing complications and reducing their rate. Heparin inhibits thromboinflammatory processes, thus could decrease neurologic impairment after cerebral air embolism. It was tested in an animal model and found to be effective only when given prophylactically in massive air emboli.[53] Barbiturates reduce cerebral oxygen consumption, lower intracranial pressure, and inhibit release of endogenous catecholamines. Due to these beneficial effects, barbiturates are sometimes used for brain protection and may be helpful in cases of cerebral air emboli.[59] Two decades ago, steroids were used to reduce cerebral edema following air emboli,[170,171] but later studies showed that corticosteroids increase ischemic injury[172] and their use is no longer recommended. Experiments using animal models showed that lidocaine improves recovery following cerebral air emboli.[173,174] Lidocaine was found to be neuroprotective also in patients undergoing cardiac surgery;[175] nevertheless, it is not part of standard care in air emboli. While the abovementioned drugs failed to improve outcome following massive air emboli, they could have a potential place in microbubble injury.

There is encouraging experimental data on fluorocarbon compounds, which have high gas-dissolving capacity, may increase oxygen delivery and help shrink gas bubbles because of their high diffusion gradient.[176,177] Other studies[27,178] have presented surfactants as a possible compound that may change bubble adhesion by altering interfacial forces and reducing bubble absorption time. These future solutions deserve testing in humans after proved efficacy and safety in animal models.

Summary

We have presented published data concerning the microbubble phenomenon and its detrimental consequences. Indeed, the microbubble event and its significance have been proved in open-heart surgery and DCS. However, it awaits clinical confirmation in other conditions such as hemodialysis and rapid fluid infusion. To date, there is a limited knowledge about the management of the microbubble events. Nevertheless, acknowledgment of the problem is the first step in the path toward finding a solution. Contemporary technology offers us tools to cope with various difficulties. The best way to utilize highly developed technology is in cooperation between scientists and engineers in search of a resolution for a recognized problem. The problem of microbubbles awaits a breakthrough technological solution that will provide their detection and elimination, facilitating better care for the patient.

Appendix

The Epstein-Plesset equation

$$\frac{dr}{dt} = -DL\frac{\bar{p}^* + 2\sigma/r}{patm + 4\sigma/3r}\left\{\frac{1}{r} + \frac{1}{\sqrt{\pi Dt}}\right\}$$

where D is the diffusivity of gas in fluid; L is the partition coefficient of gas, Patm is the atmospheric pressure, P* is the excess pressure, σ is the surface tension, r is the radius of the bubble, and t is time.

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