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Letter to the Editor

Arterial and Venous Air Emboli in Health Care

To the Editor,

FROM WHAT WE KNOW, WHAT WE ASSUME, AND WHAT WE DISREGARD

There are many risks and complexities associated with the performance of cardiac surgery. All specialists in this surgical/intensive care arena use tools and techniques to prevent and avoid even the most minute amounts of gaseous (air) microemboli from entering the patient's arterial circulation. In fact, arterial air emboli are often considered a "never event" (events that should never happen) during extracorporeal circulation, and therefore many specialized types of devices, filters, and ultrasonic detectors are used to achieve this objective. It is well documented that the prevention of arterial gaseous microemboli during cardiac surgery is vital to patient safety and improved outcomes (1–3).

When air microemboli are allowed to enter the cerebral circulation, there is always the potential for causing intraoperative/postoperative stroke, death, and neurocognitive dysfunction/delirium (depression, anger, memory loss, agitation, etc.) (2–5). It is common practice to use microembolic depth and screen filters for arterial and venous blood during cardiac surgery. Both of which are designed for removing specified sizes of air and solid microemboli, depending on the type of device used. Microbubbles greater than 40 μm in diameter are generally prevented from entering arterial blood, and microbubbles larger than 150 μm in venous blood are generally prevented from entering the extracorporeal device. Arterial microbubbles larger than 20–40 μm are considered potentially hazardous to the patient and can lead to adverse postoperative outcomes (6,7).

Outside of the cardiac operating room perfusionists use another form of life support called extracorporeal membrane oxygenation (ECMO). The use of ECMO is somewhat similar to routine cardiopulmonary bypass (CPB), but arterial or venous filters are not used to capture gaseous microemboli during the ECMO procedure. This is due to concerns over clot formation in filtration devices when they are used over long periods of time (hours, days, weeks, months) with lower anticoagulation protocols used during CPB. This is not to say the chances for arterial intravascular air/solid emboli are any less of a concern with ECMO patients. In fact, clinicians managing ECMO cases have to constantly be aware of the potential for many external air microembolic sources at the bedside. Some of these sources include the use of renal replacement therapy or dialysis machines (8), the development of bronchovenous fistulas (9), and opening stopcocks for sampling or drug administrations. Even the insertion, running, or disconnection of intravenous (IV) lines (peripheral or central) (10) can be a source of venous air due to the negative IV pressures that ECMO places on the venous circulation to enable extracorporeal blood flow.

WHAT IS KNOWN

Outside of the cardiac operating room, ex vivo studies involving IV air in small animals can be traced back to as early as 1809. But even today, the exact amount of IV air it would take to cause sudden death in a human is still unknown (11).

Slow continuous infusion of air (>.36 mL/kg/min) into the venous circulation can have a dangerous impact on the lungs and heart by blocking blood flowing through the right atrium, right ventricle, and pulmonary circulation, which can result in sudden blood pressure drops and cardiac arrest (12). It is believed that even single large injections of air into a vein (25–75 mL) can be hazardous and may result in a sudden air lock in the atrium or ventricle (13).

In addition to the obstructive nature of IV air, any amount (large or small) is unquestionably foreign to the patient's circulatory system and can result in activation of the coagulation cascade and the release of inflammatory mediators (14,15). Micro and macro air can also alter blood physiology and damage or block the cerebral microcirculation if it passes into the left side of the heart as paradoxical air emboli (PAE).

Air bubbles entering the venous circulation (intentionally or accidentally) get broken into many smaller microbubbles as they pass through the contractions of the atrial and ventricular chambers of the heart. But regardless of

the bubble size, all gaseous air bubbles have the ability to coalesce (grow in size) when they contact each other and thereby grow into much larger bubbles during their course through the venous circulation (5,16).

Once air enters blood, it is immediately treated like any other foreign substance entering our body's natural defense mechanisms and is therefore immediately coated with platelets, white cells, and protein, which subsequently increases the wall thickness of these microbubbles. Even neutrophils tend to aggregate around intravascular microbubbles in an attempt to destroy them. These cellular and protein deposits then make the air microbubble walls thicker and more difficult to break or adsorb as they pass through the circulatory system, thereby having the potential to become as hazardous as solid emboli (4,16).

During the course of air bubbles through both the arterial and venous microvasculature, they have the ability to inflict damage to the delicate intraluminal gel like endothelial protective covering called the endothelial glycocalyx layer (EGL) (17). Damage to the EGL subsequently exposes the underlying endothelial cells of the blood vessel walls. As a result, platelets adhering to a bubble's surface can aggregate at this site and result in platelet activation and thrombus formation at these exposed endothelial cell surface areas (18,19).

Reports of pulmonary edema and thrombocytopenia due to pulmonary microvascular injury caused by gaseous microbubble activity on the pulmonary endothelial surfaces are yet another concern when allowing air to enter the pulmonary circulation. Other potential causative factors of air emboli-activated pulmonary edema included neutrophil aggregation around the venous air bubbles, which can subsequently lead to microvascular permeability and pulmonary exudation (19).

WHAT IS ASSUMED

The most common assumption regarding venous air is that it is less harmful to the patient than arterial air is. Indeed, this may be true, unless that venous air passes into the left side of the heart and the arterial circulation. Generally speaking, most people therefore believe that small amounts of IV air are harmless to the patient and therefore focus on preventing large amounts of IV air because data found in animals have shown this to be potentially lethal (20).

Misinformation and personal opinions based around literature on lethal air volumes found in animals have unfortunately led to the assumption that smaller volumes of air (air bubbles) are inconsequential in humans because they will immediately be absorbed into the blood or expelled in the lungs (20). Therefore, the assumption is that bubbles in an IV line will do no harm to a patient.

Small volumes of IV air may not be lethal, but they can (and are) linked to strokes. In fact, many reports relating to strokes associated with intravascular air continue to appear in the literature (21–24). Considering the potential for air bubbles to enter the venous circulation, we have to wonder why harm associated with IV air is not taken more seriously.

Unlike the adult population, the postoperative consequences of ischemia, inflammation, or damage do not always manifest itself until later in the child's life. Neurological injury may not appear until much later in the developmental years and can manifest itself as cognitive or intellectual impairment, attentional deficit, visual deficit (spatial or motor), and speech or language delays (25).

WHAT IS DISREGARDED

There are several areas involved in diagnostic and therapeutic medicine that knowingly or passively allow the introduction of gaseous microbubbles into the patient's venous circulation. In spite of what is known about arterial air emboli and the potential for venous air emboli (VAE) to paradoxically pass into the left side of the heart, some practices use air bubbles to calculate cardiac output, diagnose the presence of a patent foramen ovale (PFO) or atrial septal defects (ASD) and ablate varicose veins.

Some foramen ovale openings do not close at birth and are thereafter called a PFO defect. PFO defects are estimated to be present in about 23–45% of adults (26) and have been reported to be important risk factor for strokes, cerebrovascular accidents, and transient ischemic attacks (TIAs). Some people know they have a PFO, but most adults do not. Therefore, these people generally go through life without problems until this opening becomes symptomatic and is subsequently diagnosed by a physician.

Peripheral IV Lines

As previously mentioned, air bubbles that enter veins through peripheral IV lines will rapidly move into the right atrium and are therefore called VAE, regardless of size of these IV air bubbles. VAE have the potential to cross over to the left side of the heart into the arterial circulation as PAE through an undiagnosed PFO/ASD, or patent intrapulmonary arterial-venous anastomoses (IPAVA) shunts that exist in human lungs (27). IPAVA shunts may also be unrecognized contributors to strokes and TIAs (28). There are also reported incidents of VAE entering the brain in a retrograde manner through the brachiocephalic-jugular veins while patients are in a sitting position, resulting in cerebral air embolism (29).

IPAVA shunts are small intrapulmonary blood vessels that do not come in contact with the air sacs in our lungs.

Due to this, they allow right ventricular venous blood (and any solid or gaseous emboli it may contain) to pass directly into the left side of the heart through the pulmonary veins. IPAVA shunts have been found to exist in approximately 22–30% of resting adults and have the potential to increase in size during exercise (27,28).

Most of the reported strokes in the United States are known to be ischemic and embolic in nature, but there are many of these ischemic strokes that are of unknown origin. Strokes of unknown origin are called cryptogenic strokes (30). One study of young adults with ischemic strokes in the United States found that 43% of the strokes investigated were found to be cryptogenic in nature (31). There are numerous studies and reports of morbidity associated with cerebral air emboli coming from peripheral IV lines, which emphasize the necessity of eliminating all IV air bubbles, regardless of personal opinions or assumed air bubble volumes in IV lines (32–36).

Bubble Study

To determine the presence or size of a PFO in symptomatic patients, physicians will perform a test called the "Bubble Study." This test is performed using a microbubble contrast that is created when combining a fixed amount of saline solution (usually 9.0 mL) and a fixed amount of air (usually 1.0 mL) in a syringe and shaking the syringe to create large amounts of small microbubbles as a contrast for injection. The microbubble contrast is then injected into a peripheral vein while either an echocardiogram or a transcranial doppler is used to detect microbubbles that have transmitted to the left side of the heart through an opening in the atrial wall (PFO or ASD). If a PFO does exist, PAE will be detected in the left atrium of the heart or in the middle cerebral artery of the brain (37). Generally speaking, the more gas emboli detected in the left atrium or middle cerebral artery, the larger the PFO.

Theoretically, in the absence of a PFO, all of the microemboli injected would stay on the right side of the heart and thereafter transit into the pulmonary artery and out through the lungs to be removed by the air sacs in the lungs, unless they are directed through IPAVA shunts. Investigators have found that cerebrovascular complications such as TIAs and strokes can occur in patients after a bubble study (38). Ischemic cerebrovascular complications can occur in patients who undergo a bubble study and are often associated with the presence of cardiac or IPAVA shunts, although the true incidence and degree of disability as a result is unknown (38).

Thermodilution Cardiac Output

Many patients in the operating room or intensive care unit have a need to be monitored for central venous pressures (CVPs) (atrial, ventricular, pulmonary, and wedge), cardiac outputs, temperatures, and saturations. Pulmonary artery catheters generally provide this information through internal jugular vein access, which then passes through the right atrium, right ventricle, and sits in the pulmonary artery. Removal of these central catheters has to be done carefully and with the patient in a supine or Trendelenburg position to increase CVP and avoid significant air entrainment into these prominent veins. However, central venous catheters are well known to be a potential source of VAE and can contribute to morbidity/mortality associated with cerebral air embolism (9,32).

The method of measuring cardiac output through a pulmonary artery catheter (e.g., Swan-Ganz) is performed by rapidly injecting 10 mL of cold saline into the proximal injectate hub of this catheter, while the exit port for the saline lies directly in the right atrium. As the cold fluid rapidly enters the atrium, two things happen. One is that a cardiac output can be calculated as this cold fluid passes over a thermistor on the catheter. The second thing that happens is the cold fluid creates a massive microbubble storm in the right atrium as this cold fluid rapidly enters this warm chamber of the heart. This can easily be seen by placing an ultrasound probe directly over the right atrium using epicardial ultrasonography during open-heart surgery (personal experience).

Little is known about the incidence of retrograde cerebral air emboli or PAE associated with this massive microembolic storm during this diagnostic procedure, because it has never been investigated. The general assumption is if microbubbles are used in bubble studies, then they must be safe in thermodilution cardiac outputs.

Foam Sclerotherapy

There are many treatment options for addressing varicose veins, but foam sclerotherapy seems to be the most popular. The making of foam for foam sclerotherapy is done by mixing (similar to a bubble study) 4.0 mL oxygen/air with 1.0 mL sclerosing agent (polidocanol, sodium tetradectyl sulphate, etc.). This mixture of sclerosing agent and foam bubbles is then injected into the patient's varicose veins (usually leg).

Even when these foam gaseous bubbles are made of oxygen and injected into a lower limb, bubbles can transit up the inferior vena cava and into the right atrium, potentially ending up as PAE if right to left shunting exists in the heart or lungs. Reports related to foam sclerotherapy have found the possibility of cerebral injury due to paradoxical emboli, and it has been suggested that several precautions should be exercised when performing this therapeutic treatment (39,40).

IV Fluid Invisible Outgassing

All IV fluids are known to contain air in a dissolved state, which can be released from the fluid in the form of air bubbles as the temperature of the fluid increases from room temperature (crystalloids) or 4°C (banked

blood and plasma) to body temperature. Depending on the rate of warming, these air bubbles are often visible in IV lines (especially blood warmers) and can be addressed. But, when colder fluids enter the patient's blood stream and quickly warm to patient temperature, IV outgassing still occurs but is invisible to the clinician. The volume of invisible air emboli released in the blood is greater with refrigerated blood products than it is with room temperature IV fluids (41). To avoid invisible outgassing and VAE, fluids should be warmed to near patient temperatures before administering, and IV-line air filters or bubble traps should be used, especially when using IV-line blood warmers (42).

The phenomenon of arterial blood and invisible outgassing should also be considered prior to the start of extracorporeal circulation, especially since these invisible arterial microbubbles may directly enter the aortic arch and the patient's cerebral circulation at the start of bypass. There have been reports of gaseous microemboli being detected during the first two minutes at the start of CPB, when using membrane oxygenators (43). To prevent invisible outgassing, warming the perfusate to near patient body temperature before starting CPB (or ECMO) is recommended.

THE CONUNDRUM

Every year, cardiac surgery programs around the globe spend millions of dollars on arterial filters, venous filters, cardioplegia filters, blood filters, ultrasonic gaseous emboli detection devices, and other intraoperative techniques to avoid and prevent the transmission of gaseous microemboli to the patient during cardiac surgery.

Considering the potential for IV air emboli occurring outside the cardiac operating room and the use of several microembolic therapeutic measures that are known to increase the potential for PAE, perhaps we should ask ourselves two questions; Are all of the embolic preventative measures, research, evidence, and money spent on preventing gaseous microemboli (in the cardiac operating room) necessary? Or is there a real need to address and re-educate those involved with all IV infusions regarding the potential morbidity/mortality associated with IV air emboli, including the potential risks of producing paradoxical and cerebral air emboli?

In addition to the human and healthcare costs associated with intravascular air emboli, healthcare litigation costs can be a concern and are known to be substantial. A 2009 review of the American Society of Anesthesiologists Closed Claims (ASACC) database found, that out of 10 categories of injury related to peripheral IV catheters, those injuries caused by air embolism had the highest payout, with a mean of $325,000 (range $25,800–$4,120,200) (44). An earlier review of the ASACC database (2004) looked at 11 claims related to air emboli injury from central and pulmonary IV catheters and found that those claims resulting in air embolism also had the highest payout with a mean of $517,125 (range $304,000–$1,076,653) (45).

IN CONCLUSION

In spite of the evidence that VAE can damage and alter the integrity of the blood vessels EGL thereafter affecting intra/extraluminal fluid movement, it appears that some clinicians still consider a little IV air will never hurt a patient, or that it would take a huge amount of IV air to cause harm. A simple search through www.pubmed.gov, using the words "air emboli AND cardiac surgery" will find over 1,118 published abstracts on the hazards of intravascular air bubbles that date back to 1945.

The responsibility for improving intrahospital patient care by preventing microembolic adverse outcomes during IV fluid therapy lies with the educational institutions, clinical training programs, and clinicians responsible for IV fluid therapy administration. This includes those growing numbers of out-of-hospital settings, where nonhealthcare professionals are delivering intravascular fluids (often referred to as Drip Bars) for a variety of reasons.

We may never eliminate all forms of VAE, but there are numerous types of disposable IV filters, air detection devices, and IV bubble traps on the market that will help prevent or minimize accidental IV air emboli. Unfortunately, these preventative tools add to costs to a healthcare system and are therefore usually used only in the intensive and critical care settings, including some pediatric patients.

Many reports refer to the morbidity and mortality associated with IV air bubbles as an uncommon or rare event. Perhaps we should determine if the arterial or venous consequences associated with air emboli are truly uncommon, or if the recognition and reporting of this event is uncommon. More emphasis needs to be placed on clinical education about the potential for strokes-associated IV air bubbles in the presence of intracardiac and extracardiac shunts. Primum Non Nocere.

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