J Forensic Sci, July 2005, Vol. 50, No. 4
Paper ID JFS2005061
Available online at: www.astm.org

TECHNICAL NOTE

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The Potential of Venous Air Embolism Ascending Retrograde to the Brain*

ABSTRACT: A bench study was performed to investigate the potential of air bubbles entering a central vein via a central venous catheter to ascend retrograde to the brain. The results support the hypothesis that air bubbles may rise retrograde against the venous blood flow, depending on bubble size, central vein diameter and cardiac output. A review of radiological findings in published case reports indicates that the occurrence of retrograde cerebral air embolism is underestimated.

KEYWORDS: forensic science, forensic radiology, air embolism, paradoxical embolism, intracranial embolism, central venous catheterization, superior vena cava, computed tomography

Venous air embolism (VAE) is a serious complication of surgical or medical therapy and may lead to death. Most episodes of VAE are related to central venous catheters (CVC), in particular when the chest is elevated (1). VAE is often diagnostically overlooked unless detected by magnetic resonance imaging or computed tomography (CT) (2).

VAE commonly occurs when non-collapsible open venous channels or CVCs are situated above the level of the heart, creating a cardio-atmospheric fistula with a negative pressure gradient driving air into the blood vessels. Once inside the venous vasculature air bubbles carry the major risks of pulmonary air embolism with consequent cardio-circulatory effects or cerebral air embolism with neurological symptoms (3–5). Cerebral air embolism following venous entry of air bubbles is generally assumed to occur paradoxically, either through a functionally patent foramen ovale or via air transit through the pulmonary vasculature. Ploner et al. hypothesized the possibility of cerebral air embolisms developing retrograde via the venous system (6).

Our study aimed to determine whether there are experimental and radiological findings to support the hypothesis that venous air embolism entering through a CVC has the potential to ascend retrograde against the venous blood flow.

Methods

Physical, Physiological and Anatomical Considerations

Due to their low specific weight air bubbles will rise to cranial in a patient sitting upright, if the rise velocity is greater than the opposing blood flow velocities in the central veins. With increasing overall cross-section of feeding veins the peripheral vein flow velocity decreases and facilitates retrograde rise of air bubbles as long as the diameter of the vein remains larger than that of the air bubble.

Air Bubble Characteristics—A rough estimate of bubble size depending on surface tension force and buoyancy force at the catheter tip is obtained by Tate's Law. The rise velocity is determined from the equilibrium between buoyancy and drag force. Using the measured drag of a sphere (7) the rise velocity was calculated for various bubble diameters.

Blood Flow Characteristics—Mean blood flow velocity in the superior vena cava (SVC) is the result of cardiac output and internal vascular diameter. Mean SVC diameter in adults is 15 to 20 mm (8). Assuming a blood flow volume in the SVC of 35% of the cardiac output (9), mean blood flow velocity was estimated for each diameter.

Experimental Setting

A bench study was carried out using a vertical silicone tube filled with citrated pig blood (hematocrit: 35%). Various diameters of 20, 18 and 15 mm were installed inside the tube (Fig. 1). Blood flow was adjusted using a standard cardio-technical pump (Multiflow Rollerpumpe, Stökert/Schiley, Munich, Germany) to simulate physiologic conditions of the SVC (35% of a 5 L/min cardiac output). A central venous catheter (CS-12123-E, ARROW International Inc., Reading, PA) was inserted through the tube wall and directed caudate. After the CVC was filled with air an attached T-bore stopcock was

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* Supported in the form of equipment by the University Department of Cardio-, Thoracic- and Vascular Anesthesiology and Intensive Care and the Institute of Biomedical Research, Medical University of Vienna, Austria.
Received 10 Feb. 2005; accepted 13 March 2005 ; published 25 May 2005.

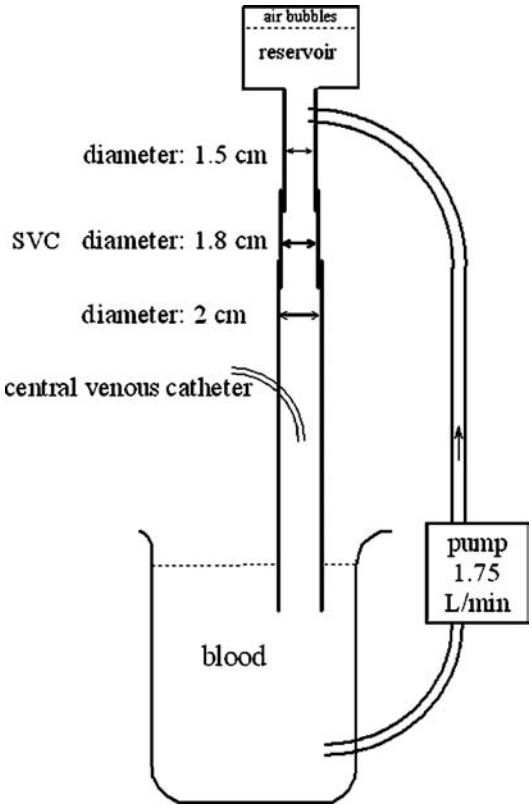

FIG. 1—*Experimental setup to study venous air embolism characteristics in the superior vena cava (SVC) with various diameters. SVC flow represents 35% of cardiac output (5 L/min).*

opened to allow air bubbles to enter via the 16-gauge distal lumen (single orifice at the catheter tip). A negative pressure (defined as the gradient between intravascular pressure and atmospheric pressure taken as 0 mm Hg) at the catheter lumen orifice was adjusted to −7 cm H_20 (−5.3 mm Hg). The behavior of air bubbles in a constant blood flow depending on the inner tube diameter was evaluated ten times for each inner tube diameter of 20, 18 or 15 mm.

Radiological Investigation

"Medline" (www.ncbi.nlm.nih.gov/pubmed) was researched to find possibly undetected retrograde cerebral venous air embolism in radiological investigations of previous published "case reports" on "cerebral air embolism" between 1991 and 2001 and meeting the following requirements: history of central venous catheter, consecutive neurological symptoms, CT-diagnosed cerebral air embolism, no diagnosed patent foramen ovale, and exclusion of neurosurgical procedures (Table 1). Published photographs were re-evaluated by a senior radiologist from the Department of Radiology of Innsbruck Medical University.

Results

Calculation of Bubble Size and Anticipated Behavior in Venous Blood Flow

Applying Tate's Law to a 16-gauge catheter yields a bubble diameter of approximately 3 mm. Calculated mean blood flow velocity for each SVC diameter and rise velocity of air bubbles in blood for the various bubble diameters are presented in Fig. 2. Our results indicate that air bubbles with a diameter greater than 1.5 mm may rise to cranial depending on cardiac output and SVC diameter. Air bubbles smaller than 1.5 mm in diameter can be carried off by the blood flow.

Experimental Investigation

The behavior of air bubbles was evaluated ten times for each diameter. Air bubbles entering through a central venous catheter (lumen: 16 gauge) into an upright tube with circulating pig blood rose retrograde at SVC diameters of 20 or 18 mm, but not at a SVC diameter of 15 mm.

Radiological Investigation

"Medline" screening revealed 48 case reports on cerebral air embolism published between 1991 and 2001; six of them met our inclusion criteria (Table 1). Re-evaluation of published CT scans did not confirm air embolism in cerebral arteries, as could be expected from paradoxical embolization. The areas of air appear too large in diameter to be situated in the cerebral arterial system. Hence, the presence of retrograde cerebral air embolism can be considered an alternative cause in all cases.

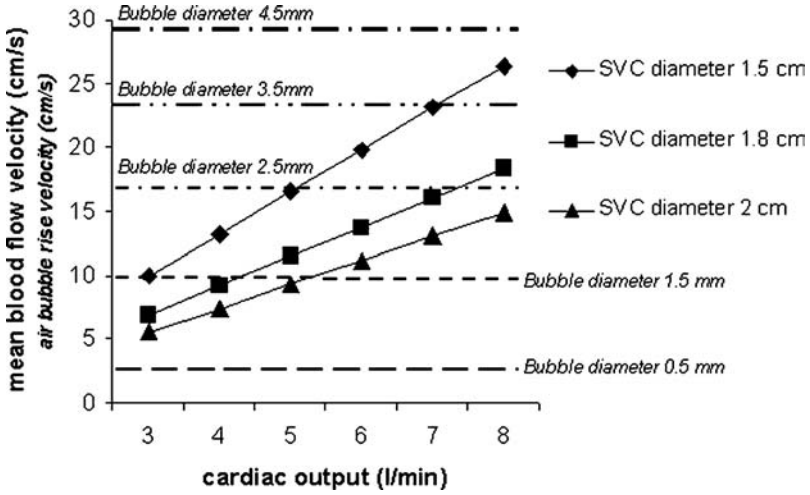

FIG. 2—*The connected symbols show the calculated mean blood flow velocity for various superior vena cava (SVC) diameters depending on cardiac output. The horizontal lines indicate the rise velocity of air bubbles in blood for the designated bubble diameters.*

TABLE 1—*Clinical case reports on venous air embolisms from central venous catheters (CVC), which resulted in assumed paradoxical cerebral air embolism. In all cases, a retrograde cerebral air embolism could be considered as an alternative cause, since the areas of air seen on the published computer tomography (CT) scans appear too large in diameter to be situated in the cerebral arterial system.*

Case Report	Manipulation Position *Echocardiography*	Case Report Authors' CT Scans Description	Case Report Authors' Diagnosis	Innsbruck Authors' Differential Diagnosis
Heckmann et al. (5)	Unintentional disconnection of CVC. Position not mentioned. *No intracardial defect on ventriculography.*	1st day: air bubbles in the right hemisphere subarachnoidal vessels. 3rd day: hypodense lesion of the right. hemisphere	Paradoxical cerebralp air embolism.	Retrograde cerebral air embolism.
Moorthy et al. (14)	Removal of right internal jugular CVC (pulmonary artery catheter). 15° head-up position. *No intracardial defect on echocardiography.*	Air bubbles in the right frontal and parietal cerebral circulation.	Paradoxical cerebral air embolism.	Retrograde cerebral air embolism.
Dilkes et al. (15)	Insertion of right subclavian CVC (Hickman). Supine position. *Echocardiography not mentioned.*	1st day: multiple right cortical air emboli. 14th day: infarct corresponding to sites of air embolism	Paradoxical cerebral artery air embolism.	Retrograde cerebral air embolism.
Schlotterbeck et al. (16)	Unrecognized disconnection of stop-cock. Elevated thorax. *No intracardial defect on echocardiography.*	1st CT: multiple air bubbles (2–10 mm) subcortical in both hemispheres. 2nd CT: swelling and hypodense lesion of the complete right hemisphere.	Paradoxical cerebral air embolism.	Retrograde cerebral air embolism.
Pham et al. (17)	Removal of right internal jugular CVC. Sitting position. *Echocardiography not mentioned.*	1st day: Air bubbles in the left frontal lobe parenchyma and in the subarachnoidal space in the sulci on both sides. 4th day: ischaemia in the former embolised areas.	Paradoxical cerebral air embolism.	Retrograde cerebral air embolism.
Inamasu et al. (18)	Insertion of right subclavian CVC. Position not mentioned. *Echocardiography not mentioned.*	1st day: air bubbles in the right parietal lobe, in the periphery of the middle cerebral arteries. 2nd day (MRI): cerebral infarction in the right motor cortex.	Paradoxical cerebral air embolism in the middle cerebral arteries.	Retrograde cerebral air embolism

Discussion

Our experimental investigation supports the hypothesis that air bubbles entering the venous circulation via a central venous catheter have the potential to rise retrograde depending on air bubble size and local blood flow velocity. Taking into account the fact that bubble diameter may vary significantly, depending on the position of the catheter tip and local flow conditions, we conclude that a 16-gauge catheter tip produces air bubbles of more than 1.5 mm in diameter. Based on the fact that peripheral vein flow velocity decreases with the increase in overall cross-section of feeding veins, we conclude that air bubbles entering via a CVC may rise to the brain, as long the vein lumen diameter is larger than that of the air bubble. Our findings support the hypothesis previously set forth by Ploner et al. (6). The hypothesis is also supported by another case report (10) and by the findings of two studies, describing ascending asymptomatic venous air embolism after injection of intravenous fluids. Numerous venous air emboli in the head and neck veins were detected in various locations of the venous system such as the internal jugular vein, cavernous sinus, frontal or temporal scalp, infratemporal fossa, superior ophthalmic vein, straight sinus and the superior sagittal sinus (11,12). Furthermore, re-evaluation of published CT scans from six case reports with presumed paradoxical cerebral air embolism, could not exclude the possibility of retrograde cerebral air embolism.

Occluding air bubbles in the cerebral venous system obstruct blood flow and likely result in symptoms similar to a cerebral vein thrombosis. Ploner et al. (6) reported resorption of the areas formerly representing air bubbles and development of massive cerebral edema in computer tomography on the third day after retrograde cerebral VAE had occurred. The exact pathophysiological mechanisms of retrograde cerebral air embolism should be

subject to further investigation. In vivo experiments are indispensable, but the local vascular anatomy of animals differs from that of humans. Some animal experiments on air bubbles in cerebral arteries have been performed (13) and we propose that further experiments should be carried out under the conditions of venous blood flow velocities, venous vascular diameters and central venous catheter-related air bubbles. Furthermore, we recommend that an international database be set up for the documentation of all central venous catheter-related VAE episodes. Documentation should include an exact history of the patient's position, catheter manipulation, neurological symptoms, any cranial computer tomography performed immediately after the event, follow-up controls, and echocardiographic exclusion of intracardiac shunts. Detailed diagnosis of VAE should be performed with enhanced CT technique (2).

There are several limitations to our investigation. The experimental model, while demonstrating general principles of fluid dynamics, fails to account for many important in-vivo factors, including venous distension and collapse, variable effects of respiration on venous flow and pressure, and regional flow patterns and turbulence particularly around venous bifurcations or confluence. Moreover the aggregate effect of flow patterns of cranial and extracranial veins must be given consideration. We did not test what happens to air bubbles in the SVC at thorax angles smaller than 90°. We anticipate that under these conditions buoyancy would force bubbles towards the SVC wall, where blood velocity is slower. When air bubbles adhere to the vessel wall, they may coagulate and, forced by the enhanced buoyancy, eventually move upward.

Not all reviewed case reports mentioned an upright patient position or consistently employed transesophageal echocardiography. Thus, the most common and important risk factor for paradoxical embolization, namely inter-atrial communication such as a patent foramen ovale (PFO) or perforated atrioseptal aneurysms, cannot be excluded in all cases.

In conclusion we here show, that air bubbles entering the superior vena cava through a central venous catheter can rise retrograde against the blood flow, depending on bubble size, superior vena cava diameter and cardiac output. Clinical and radiological findings indicate that air bubbles can further ascend retrograde to the brain. Whenever central venous catheter-related venous air embolism is followed by neurological sequelae, retrograde cerebral air embolism should be considered a differential diagnosis to paradoxical arterial air embolism in the brain.

Acknowledgments

We thank Dr. Alexander Chesi, Basel, Switzerland, for his valuable advice during preparation of the manuscript.

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