Aspects of Mechanical Ventilation Affecting Interatrial Shunt Flow During General Anesthesia

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Intraoperative transesophageal echocardiography was used to study the incidence of flow-patent foramen ovale in 33 normal, healthy patients (ASA physical status I) undergoing general anesthesia in the supine position for nonthoracic surgical procedures. Echocardiographic contrast was injected intravenously during mechanical ventilation in the presence of 0, 5, 10, 15, or 19 cm H_2O positive end-expiratory pressure (PEEP). A final test was performed during the release of 19 cm H_2O PEEP. The presence of a flow-patent foramen ovale was detected when the injected echo targets were observed crossing the interatrial septum from right to left. Most interesting, 3 of 33 patients developed a right-to-left shunt that was first detected with the steady application of 10 (1 patient) or 15 cm H_2O PEEP (2 patients). In all three cases, the shunt flow was accentuated on the release of PEEP; however, no additional cases were detected using this respiratory maneuver. These cases represent the first demonstration of right-to-left interatrial shunting evoked as the result of the sustained application of PEEP. This study also revealed a lower than expected incidence of flow-patent foramen ovale (9%) when measured during general anesthesia and positive pressure ventilation with or without PEEP.

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The incidence of venous air embolism (VAE) during general or regional anesthesia in the supine position has been reported for a variety of surgical procedures, including craniectomy (41%–66%) (1,2), cesarean section (50%) (3), and hip replacement surgery (30%) (4). Although the likelihood of VAE during these procedures is substantial, clinical manifestations of VAE are often undetectable, because the volume of embolized air is small and the filtering capacity of the lungs is rarely exceeded.

Paradoxical VAE can occur when air crosses from the systemic venous to the systemic arterial circulation without passing through the pulmonary capillary filter. Most commonly, crossover is believed to occur through a patent foramen ovale (PFO). On the basis of an extensive autopsy series (5), the incidence of probe-PFO in an adult population is 27% (range 19%–36%), with the highest incidence found during the first three decades of life. Thus, a significant percentage of patients, as high as 24% (i.e., 36% of the 66% incidence of VAE seen in supine craniectomies), undergoing selected surgical procedures in the supine position are at risk for paradoxical VAE, with its consequent risk of cerebral or myocardial embolization and infarction (6,7).

The preoperative identification of patients at risk for paradoxical VAE has been the subject of several recent echocardiographic studies that reported prevalence rates of 6%–18% (7–10). However, the sensitivity and specificity of precordial echocardiography in preoperative screening may not be adequate to identify every patient at risk for paradoxical VAE (11,12). For example, several studies utilizing screening tests with precordial Doppler failed to identify patients in whom paradoxical embolism did occur (9,13,14). Although the relative merits of the various preoperative screening methods can be debated, it is clear that high priority should be given to the identification of those factors that can affect interatrial shunt flow in the anesthetized patient. In this way, it may be possible to enhance patient safety while minimizing the need for preoperative screening tests.

The use of mechanical ventilation with or without positive end-expiratory pressure (PEEP) is common during general anesthesia and in the intensive care unit setting. The release of high levels of PEEP (analogous to the release of a Valsalva maneuver) can evoke shunt flow through a PFO. Unknown, how-

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ever, is the extent to which cyclic intrathoracic and airway pressure changes produced during mechanical ventilation may repeatedly mimic the pressure changes produced on the release of PEEP. Thus, it is possible that mechanical ventilation may produce recurring opportunities for right-to-left interatrial shunt flow with the attendant risk for paradoxical embolization.

The goals of the present study were (a) to examine the effects of mechanical ventilation and sustained PEEP on the occurrence of right-to-left interatrial shunt flow during general anesthesia in a healthy patient population undergoing general surgery, and (b) to describe the incidence of PFO using a traditional respiratory maneuver (PEEP release) and transesophageal echocardiography (TEE) in this same population.

Methods

This study was approved by the Stanford University Medical Committee for the Protection of Human Subjects in Research, and written consent was obtained from all subjects. Thirty-three patients (13 male, 20 female; mean age 32 yr; range 21–55 yr; ASA physical status I) scheduled for nonthoracic surgery in the supine position were included in this study. Excluded from this study were patients with any history of cardiovascular, pulmonary, or esophageal disease. The conduct of anesthesia was left to the judgment of each patient's attending anesthesiologist, who played no part in the study. Typically, anesthesia was induced with thiopental (3–5 mg/kg IV) and maintained with a combination of isoflurane in an oxygen/nitrous oxide mixture. Tracheal intubation was accomplished after administration of a muscle relaxant, and muscle relaxation was maintained with a nondepolarizing agent. Routine monitoring included electrocardiography, noninvasive blood pressure monitoring, pulse oximetry, capnography, and mass spectrometry.

All ultrasound recordings were obtained using a Hewlett-Packard ultrasonograph (model Sonus 500, Andover, Mass.) with a 5-MHz single-plane transducer mounted at the tip of a 14-mm flexible adult gastroscope (model 21362A, Hewlett Packard echoscope). All studies were performed within the first hour of general anesthesia, with the patient in a supine position. The TEE probe was introduced into the esophagus with the transducer facing anteriorly. Tomographic planes were obtained in the usual fashion by translating and rotating the echoscope within the esophagus while observing the ultrasonic image for reference (15). Modified four-chamber (biatrial) views were used to allow optimal visualization of the interatrial septum and left and right atria. All of the echocardiographic examinations were performed by experienced echocardiographers.

Each subject was tested during the sustained application (>30 s) of 0, 5, 10, 15, and 19 cm H_2O PEEP during mechanical ventilation using a tidal volume of 10–15 mL/kg at a frequency of 6–10 breaths/min. The final test was performed during the release of 19 cm H_2O PEEP. Echo contrast was produced by the vigorous agitation of 10 mL of saline with a small volume of air using a two-syringe technique (creating microbubble echo targets). After excluding macroscopic bubbles, the saline was rapidly injected into a peripheral vein of an upper extremity. A contrast injection was deemed adequate only if the right atrium became completely opacified by echo targets. This often required more than one injection. A test was considered positive if injected echo targets were observed to cross the interatrial septum from right-to-left. All TEE data were recorded on videotape and subsequently analyzed by an independent echocardiographer.

Results

Right-to-left interatrial shunt flow was observed in 3 (9%) of 33 healthy patients during mechanical ventilation and general anesthesia for noncardiac surgery (Figure 1). In one of these patients, as previously presented in a case report (16), episodic interatrial shunt flow was observed coincident with early inspiration at 0, 5, and 10 cm H_2O PEEP, becoming independent of respiratory phase at higher levels of PEEP. Shunt flow in the other two patients was not observed in the absence of PEEP, but was first detected during the steady application of 10 and 15 cm H_2O PEEP. In these two cases, there was no obvious relationship between the septal crossing of echo targets and a specific phase of the respiratory or cardiac cycles. In the remaining 30 patients, there was no evidence of interatrial shunt flow during mechanical ventilation without PEEP or with constant PEEP up to 19 cm H_2O. The release of high levels of PEEP, a traditional respiratory maneuver used to provoke interatrial shunt flow in a manner analogous to Valsalva release, failed to permit TEE detection of any additional patients with PFO.

The three patients testing positive for flow-PFO could not be distinguished from the other 30 patients on the basis of anesthetic technique, surgical procedure, airway pressures during mechanical ventilation, or any other monitored variable. Additionally, TEE measurements of right atrial and ventricular dimensions in these patients were within normal limits.

Direct verification of PFO in our patient population was not possible, and thus an estimation of the true

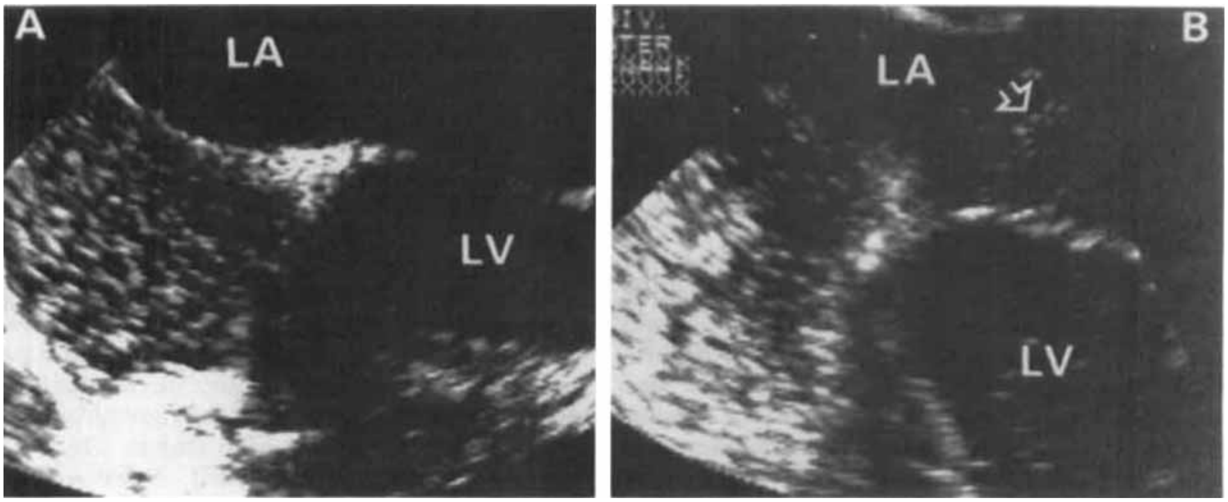

Figure 1. Transesophageal echocardiogram of a patient (**A**) during intermittent positive pressure ventilation and (**B**) during the application of 10 cm of positive end-expiratory pressure. *Arrow*, targets in the left atrium (LA) denoting interatrial shunting; LV, left ventricle. *Unlabeled chambers in the lower left corner* filled with echo targets are the right atrium and right ventricle.

detection rate of TEE for PFO was beyond the scope of this study.

Discussion

The ability to identify patients at risk for paradoxical embolization through a PFO and to characterize specific factors that affect flow through a PFO are of considerable interest to anesthesiologists. Previously reported preoperative screening studies using precordial (transthoracic) echocardiography have been characterized by both low sensitivity and false-negative results (7,14). Contrast imaging with TEE is superior to transthoracic imaging for the detection of PFO (11). Pearson et al. (11) studied 79 patients presenting with unexplained stroke or transient ischemic attacks and compared transthoracic echocardiography with TEE. A PFO was more frequently identified by TEE (9 vs 1 of 79 patients; $P < 0.005$). In a similar study at our institution (12), 4 of 50 patients with recent transient ischemic attack or embolic stroke and normal transthoracic echocardiograms had TEE-detectable PFOs. These findings, confirmed by other investigators (15), demonstrate that contrast two-dimensional (single-plane) TEE is presently the definitive diagnostic technique for PFO detection. The possibility that the single plane of view afforded by two-dimensional TEE may miss crossing echo targets remains of some concern. Recently, biplane and omniplane TEE probes have been introduced into clinical practice (17). Future studies may demonstrate that these devices can enhance the visualization and detection of PFO.

Konstadt et al. (18), in a recently published study of 50 patients with severe cardiovascular disease, using both TEE and Doppler techniques, reported a 26% incidence of *flow*-PFO. These results closely approximate the overall prevalence of *probe*-PFO (25%–27%) from autopsy studies (5,19), and this is the only echocardiographic study to demonstrate this high sensitivity. In the present study, using techniques very similar to those of Konstadt et al. (18), the incidence of flow-PFO in a healthy general surgical population was only 9%. The respiratory maneuver used to provoke shunt flow (release of 19–20 cm H_2O positive airway pressure) was similar in both studies. Konstadt et al. (18) attributed the high detection rate of their TEE technique to four factors that distinguished their study from those previously reported. The first three factors were identical in both studies. Specifically, the heart was imaged using a biatrial view to provide optimal visualization of the interatrial septum (20); second, a vigorous two-syringe technique was used to agitate the saline for the production of high-density microbubble echo targets; and third, complete opacification of the right atrium was assured before a test was considered valid. The fourth factor was their use of pulse-wave and color-flow Doppler techniques. Using these techniques, they were able to detect right-to-left interatrial shunt flow in one additional patient with shunt flow previously undetected by conventional contrast TEE. Overall, however, the color flow Doppler was found to be a much less sensitive technique, detecting only 3 of the 12 patients with right-to-left interatrial shunting (18).

In the absence of any significant technical or operator differences, we believe that the uniquely high detection rate of TEE in the Konstadt et al. (18) study may be related simply to differences in patient populations and the small sample size in both studies. In the present study, only healthy adults undergoing elective nonthoracic surgical procedures were included. In contrast, the Konstadt et al. (18) study patients all had evidence of cardiovascular disease, with 45 of the 50 patients (and 11 of the 12 patients with right-to-left shunt flow) presenting for coronary revascularization or valve replacement, or both. Perhaps myocardial function was altered in these patients in a way that could increase the probability for reversal of the normal left-to-right interatrial pressure gradient or could affect the normal valve characteristics of a probe-PFO. Although these patients should have elevated left atrial pressures, subtle changes in atrial dimensions, myocardial contractility, or conduction pathways may have offsetting effects on the instantaneous interatrial pressure gradient and thus on the functional patency of the foramen ovale.

Anatomic or probe patency, although necessary, may not be sufficient to ensure the physiologic or flow patency of the foramen ovale. The unidirectional flap-valve nature of the foramen ovale requires at least the transient reversal of the normal left-to-right interatrial pressure gradient to permit shunt flow. Persistent reversal of this interatrial pressure gradient is usually associated with right heart outflow obstruction and right atrial volume overload. Transient reversal of the gradient can occur with release of sustained airway pressure (e.g., after a Valsalva maneuver or the release of PEEP). During the strain phase of a Valsalva maneuver or during the sustained application of PEEP, intrathoracic pressure increases, transiently causing right atrial pressure to decrease (secondary to decreased venous return). Then, on release of the Valsalva maneuver or PEEP, venous return to the heart suddenly increases, causing a transient increase in right atrial pressure (as much as 20 mm Hg) (21) with the potential for reversal of the normal interatrial pressure gradient. Langholz et al. (22) recently identified in three patients three different mechanisms for right-to-left flow through a PFO in the absence of elevated pulmonary artery or right atrial pressures: (a) transient reversal of the normal interatrial pressure gradient with each cardiac cycle; (b) preferential streaming of superior vena cava blood entering the right atrium directed at the foramen ovale, producing a localized increase in pressure at that site sufficient to permit shunt flow; and (c) release of 20 cm H_2O PEEP, causing right atrial pressure to increase above left atrial pressure. It is likely that the first two mechanisms operate continuously in all normal persons to at least reduce the magnitude of the interatrial pressure gradient and thus increase the probability of right-to-left shunt flow. For example, in the patient exhibiting the second mechanism described by Langholz et al. (22), the superior vena cava blood flow was directed at the foramen ovale as the result of a large right atrial mass; however, in normal adults, blood returning to the heart via the inferior vena cava is normally directed at the foramen ovale as a persistent anatomic consequence of fetal circulation. Thus, the generation of highly localized atrial septal pressure zones occurs normally but would be difficult to measure by conventional techniques.

The capacity of provocative respiratory maneuvers to cause paradoxical shunt flow may depend simply on the magnitude of the pressure gradient across the foramen ovale at the time of testing. For example, patients with small gradients may exhibit pressure reversals with each respiratory or cardiac cycle (23), whereas in others with large gradients, even the release of 20 cm H_2O PEEP or a Valsalva maneuver may not produce a sufficient increase in right atrial pressure to cause reversal of the normal interatrial gradient.

Somewhat more difficult to explain mechanistically is our observation that the sustained application of PEEP at 10–15 cm H_2O during mechanical ventilation was sufficient to permit right-to-left interatrial shunt flow in all three patients testing positive for flow-PFO using standard respiratory maneuvers. This observation may be explained by hypothesizing that sustained positive airway pressure will eventually increase right atrial pressure relative to left atrial pressure, possibly through an effect on pulmonary vascular resistance, thereby further reducing or reversing the interatrial pressure gradient. Perkins and Bedford (24) reported that right atrial pressure was increased by the application of 10 cm H_2O PEEP and exceeded pulmonary artery wedge pressure (and, by inference, left atrial pressure) in 7 of 11 patients studied while anesthetized in the sitting position. However, more recent studies in both humans (25) and dogs (26) failed to demonstrate any significant effect of 10 cm H_2O PEEP on the absolute interatrial pressure gradient, although 20 cm H_2O PEEP did reverse the interatrial pressure gradient in one of eight patients tested (25). A complete understanding of the factors affecting interatrial pressure gradients will require additional study.

In summary, we have reported the first demonstrations of right-to-left shunt flow evoked as a result of the sustained application of PEEP during general anesthesia. Our results suggest that patients exhibiting intrinsic PEEP or any patient on mechanical ventilation and especially those patients requiring PEEP, such as those in an intensive care unit setting, may be at increased risk for paradoxical embolization after the inadvertent introduction of even small quantities of air at a wound or vascular access site. Furthermore, we would not advocate the use of PEEP in an attempt to decrease the risk of VAE because of the probable increased risk for paradoxical embolization. Finally, we believe that the conventional respiratory maneuvers used to evoke interatrial shunt flow are inadequate in many cases. The ideal provocative maneuver should mimic the changes induced by VAE, specifically producing a sudden increase in pulmonary artery pressure with consequent increase in right heart pressures and subsequent decrease in left heart pressures. Future studies should focus on mechanisms that control the physiologic patency of the foramen ovale. This information will be of considerable clinical importance in the intraoperative and intensive care unit management of many patients.

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