Paradoxical air embolism in pigs with a patent foramen ovale

A. VIK, B. M. JENSSEN, and A. O. BRUBAKK

Department of Biomedical Engineering, University of Trondheim, Center of Medical Technology, 7005 Trondheim, and Sintef Unimed, 7034 Trondheim, Norway

Vik A, Jenssen BM, Brubakk AO. Paradoxical air embolism in pigs with a patent foramen ovale. Undersea Biomed Res 1992; 19(5):361-374. Recent studies have indicated that divers with a patent foramen ovale (PFO) are at risk of developing some forms of decompression sickness. Thus, the objective of the present study was to investigate if the occurrence of paradoxical air embolism (PAE) was enhanced in pigs with a PFO compared to the occurrence in pigs without such a defect. Out of 54 pigs, 18 had a PFO (group PFO), and the other 36 composed the controls (group C). The pigs were anesthetized, mechanically ventilated, and received venous air infusion at four different rates (0.050, 0.075, 0.100, and 0.200 ml·kg⁻¹·min⁻¹). PAE was monitored by use of a transesophageal echocardiographic probe to detect if any arterial air bubbles were present in the left atrium or the aorta. We found that PAE appeared at a lower infusion rate in group PFO than in group C. When PAE occurred, the mean pulmonary arterial pressure and the mean arterial pressure were significantly higher in pigs with a PFO than in the control pigs. Finally, the infused air volume per kilogram of body weight in group PFO was significantly lower than that observed in group C. The results demonstrated that the risk of PAE occurring in mechanically ventilated pigs with a PFO was greater compared to the risk observed in pigs without a PFO.

<table>
<thead>
<tr>
<th>swine air embolism</th>
<th>congenital heart defect</th>
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<tr>
<td>paradoxical air embolism</td>
<td>patent foramen ovale</td>
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<td>decompression sickness</td>
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Arterial gas embolism may be the result of either direct injection of gas bubbles into the arteries during the course of various medical investigations or treatments (1), or the result of venous gas bubbles reaching the arterial side of the circulation. The latter case is termed paradoxical air embolism (PAE), and observations during various therapeutic procedures (2, 3), as well as during experimental studies (4–9), have demonstrated the possibility of venous gas bubbles becoming arterialized. PAE occurs if gas bubbles pass through the pulmonary circulation (5–9) or if they pass via connections within the heart (2, 4, 10, 11), usually a patent foramen ovale (PFO).

Barotrauma of the lungs of divers, during their ascent to the surface, may permit gas bubbles to escape into the pulmonary veins and thence into the arterial circulation (12). Otherwise, arterial bubbles observed in divers (11, 13) have generally been
assumed to be due to PAE resulting from inert gas bubbles being liberated from the peripheral tissues and venous blood during decompression. The importance of intravascular bubbles, and thereby of PAE, in decompression sickness has still not been elucidated. However, recent studies (14, 15) have suggested an increased risk of some forms of decompression sickness occurring in divers with a PFO.

In previous studies (8, 9) we demonstrated that the lung circulation in the pig is an excellent filter for gas. In those studies we had to exclude more than 30% of the pigs after the experiments because a PFO was diagnosed at autopsy. However, the experiments suggested that a PFO was an important mechanism for PAE occurrence. The aim of the present study was therefore to compare the incidence of PAE, during venous air embolism, in pigs with a PFO with the incidence in control pigs. Furthermore, we wished to test the hemodynamic changes as well as the infused volumes of air at the time of arterial bubble detection in the two pig populations.

MATERIALS AND METHODS

Surgical procedure

Fifty-four domestic farmyard pigs (2–3 mo. of age, body weight 18–32 kg, 23 ± 3.0 kg, SD) were used as experimental animals in this study. The pigs were fasted for 16 h, with free access to water. Fifteen to 20 min before induction of anesthesia, the pigs received premedication: 7–9 mg/kg azaperonum (Sedaperon, Janssen) intramuscularly. Pentobarbital sodium was thereafter given intravenously (25–35 mg · kg⁻¹) via an ear vein, and the induced anesthesia was maintained by a continuous i.v. infusion (5–15 mg · kg⁻¹ · h⁻¹). A tracheotomy was performed, and the animals were ventilated in the supine position using a volume-regulated respirator (model no. 613, Harvard Apparatus, South Natick, MA). A tidal volume of 7–11 ml · kg⁻¹, a frequency of 10–16 breaths · min⁻¹, and an oxygen content of the air mixture of 25–35% were used. The urinary bladder was drained through a cystostomy. Body temperature was monitored by a rectal probe (Exacon, MC 8700) and maintained at 37.5°–38.5°C using a heating pad.

The right ventricle and the pulmonary artery were catheterized via the jugular veins, using polyethylene tubing (0.76 mm i.d.). The former functioned as an air infusion catheter, whereas the latter measured pulmonary arterial pressure. In 7 of the pigs with a PFO, the infusion catheter was positioned in the right atrium after withdrawal from the right ventricle. The placement was verified by pressure measurement, and the catheter was withdrawn another 1–2 cm to ensure optimal positioning in the atrium. In 30 pigs an additional polyethylene catheter (0.76 mm i.d.) was introduced into the right atrium for measurement of right atrial pressure. A polyvinyl catheter (7F) was inserted into the right femoral artery and advanced into the abdominal aorta for continuous monitoring of arterial pressure. All pressures were recorded using Statham P231D transducers, which were calibrated against a mercury manometer, with zero pressure referred to the left ventricular mid-level. The right femoral vein was cannulated with a polyvinyl catheter (7F) to provide venous access for fluid infusion (0.9% NaCl, 12–18 ml · kg⁻¹ · h⁻¹). Arterial blood was sampled from the aortic catheter, and gas tensions were analyzed using an IL 1306 pH/blood gas analyzer (Instrumentation Laboratories, MA). At least 30 min were allowed to elapse.
for stabilization after the surgery had been completed. During the initial part of this period, the respirator frequency and tidal volume were adjusted to keep the arterial \( \text{PO}_2 \) (\( \text{PaO}_2 \)) between 105 and 135 mmHg and the arterial \( \text{PO}_2 \) (\( \text{PaCO}_2 \)) below 42 mmHg. Baseline data were recorded during the following half-hour period.

**Bubble detection**

A transesophageal echocardiographic probe (TEE 7.5 MHz) interfaced with a CFM 700 color flow scanner (Vingmed A/S, Horten, Norway) was inserted and positioned to obtain a simultaneous, two-dimensional view of the right pulmonary artery and the left atrium (Fig. 1A) or of the pulmonary artery and the aorta (8). This ultrasound image made it possible to detect the bubbles when they emerged into the left side of the heart either from the pulmonary veins or from the right atrium (Fig. 1B), indicating

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Fig. 1. *Top*, ultrasound image of the left atrium (LA) with PFO constituting a channel (asterisk) in the atrial septum. PFO diameter 1.5 mm. RA, right atrium; PV, pulmonary vein; RPA, right pulmonary artery. *Bottom*, same ultrasound image after air infusion started. High intensity spots (arrows) indicate the presence of several air bubbles in the right pulmonary artery and in the left atrium of one bubble that has emerged through the PFO. Right atrium can be seen to bulge into the left atrium, and the diameter of the pulmonary vein is reduced.
the onset of PAE. The ultrasound images were stored on videotape during all infusion periods.

Air infusion

Air was infused continuously through the right ventricular catheter or right atrial catheter (0.76 mm i.d.), and the infusion was controlled by a calibrated flowmeter. Infusion rates of 0.050, 0.075, 0.100, and 0.200 ml ⋅ kg⁻¹ ⋅ min⁻¹ were used. The bubbles had a diameter of approximately 2 mm when infused into stationary water. However, it was not possible to determine the size of the bubbles when they entered the pulmonary circulation because both the rate of flow at the infusion site and any mixing in the ventricle will have influenced the size distribution (16).

Experimental procedure

During experiments to study the transpulmonary passage of gas in the pig (8, 9), we observed a high incidence of PFO. The hearts of all pigs were investigated at autopsy after the experiments. When a PFO was diagnosed either during the infusions or always at autopsy, the pig was excluded from the previous studies and was included in this report to form group PFO. Consequently, the animals without a PFO from these earlier studies serve as controls in the present study. In addition, another 22 pigs are included, of which 15 received a surfactant, Pluronic (Fluka Chemie AG, Buchs, Switzerland), for other unrelated studies. This drug did not seem to alter hemodynamic variables measured in this study or the incidence of PAE after transpulmonary passage (unpublished observations). The protocol was the same during all experiments, except for the positioning of the infusion catheter: Seven of the pigs with a PFO had a right atrial catheter, whereas the remainder of the pigs with a PFO and all the control pigs had a right ventricular infusion catheter.

Eighteen pigs with a PFO (group PFO) received air at a rate of 0.050, 0.075, 0.100, and 0.200 ml ⋅ kg⁻¹ ⋅ min⁻¹. Eleven pigs received only one infusion. In the remaining 7, the infusion was terminated as soon as bubbles were detected in the left atrium, because the bubbles could be observed when they emerged through a PFO. The PFO then constituted a "channel" in the atrial septum of the ultrasound image (Fig. 1). The infusion catheter was thereafter withdrawn from the right ventricle to reach the right atrium, as verified by pressure measurement, to study PAE during atrial infusions. The animals were allowed to recover for a minimum of 20 min. The intravascular pressures and blood gases had by then either returned to the baseline values or had remained unchanged for at least 5 min. We then proceeded with the next study condition, which included infusion of air at the lowest infusion rate (0.050 ml ⋅ kg⁻¹ ⋅ min⁻¹) if this rate was not the one that had already been used. The infusion was terminated when PAE was observed, or, if no arterial bubbles were detected, the air infusion was terminated after the pressures became stabilized, but always ≤ 30 min. At least 20 min were again allowed to elapse for a return to baseline values or for stabilization of intravascular pressures and blood gases, whereafter the pigs received air at successive higher infusion rates. The same procedure with respect to termination of continuous air infusion and stabilization, between each infusion as described above was used. Because the mean arterial pressure (MAP) often did not return to the baseline values during the recovery periods, no infusion was started unless
MAP reached at least 70 mmHg. Thus, most of the 7 pigs that received repeated 
embolizations received only 3 infusions. A total of 32 infusions were given to the 18 
pigs with a PFO, 18 of these were right atrial infusions (group PFO\textsubscript{RA}), and 14 were 
right ventricular infusions (group PFO\textsubscript{RV}).

Thirty-six pigs without a PFO acted as controls (group C) in the experiments. Air 
was infused at rates of 0.050 (22 pigs), 0.100 (5 pigs), and 0.200 ml \cdot kg\textsuperscript{-1} \cdot min\textsuperscript{-1} 
(9 pigs) into the right ventricle. The air infusions lasted 30 min and these animals 
received only a single infusion.

The hearts of all pigs of both group PFO and group C were investigated at autopsy, 
and the diameter of any opening in the atrial septum was measured in millimeters. 
The presence of a PFO in this study was therefore based on the findings at autopsy.

Statistics

Fisher’s exact test (one-tailed) was used to compare incidence of PAE in group 
PFO and group C. To test if there were any significant changes in intravascular 
presures when arterial bubbles appeared, analysis of variance and subsequent Student’s t test with Bonferroni correction for multiple comparisons were used. 
Furthermore, differences in intravascular pressures and infused volume of air between groups 
were tested by the same procedure. Spearman’s rank correlation ($r_s$) was used to test 
any significance of correlation between PAE time and infusion rate. $P < 0.05$ was 
defined significant. Values are presented as means $\pm$ SD.

RESULTS

Incidence of paradoxical air embolism

The incidence of PAE tended to be higher in group PFO than in group C during all 
infusion rates (Table 1). During the infusion at the lowest rate (0.050 ml \cdot kg\textsuperscript{-1} \cdot min\textsuperscript{-1}) 
the difference was significant for both group PFO\textsubscript{RA} and group PFO\textsubscript{RV} when they 
were compared with group C ($P = 0.010$ and $P = 0.019$, respectively). Furthermore,

<table>
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<tr>
<th>Infusion Rate, ml \cdot kg\textsuperscript{-1} \cdot min\textsuperscript{-1}</th>
<th>Group PFO\textsubscript{RA}</th>
<th>Group PFO\textsubscript{RV}</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.050</td>
<td>3/7* (43%)</td>
<td>2/4* (50%)</td>
<td>0/22 (0%)</td>
</tr>
<tr>
<td>0.075</td>
<td>4/5 (80%)</td>
<td>$-^c$</td>
<td>$-^c$</td>
</tr>
<tr>
<td>0.100</td>
<td>4/5 (80%)</td>
<td>1/1</td>
<td>3/5 (60%)</td>
</tr>
<tr>
<td>0.200</td>
<td>1/1</td>
<td>9/9 (100%)</td>
<td>6/9 (67%)</td>
</tr>
<tr>
<td>Total infusions</td>
<td>18</td>
<td>14</td>
<td>36</td>
</tr>
</tbody>
</table>

\*The infusion catheter was positioned in the right atrium in group PFO\textsubscript{RA} and in the right ventricle in 
group PFO\textsubscript{RV} and group C.  
$^\dagger P < 0.02$ compared to control group.  
$^c$No animals were tested at this 
infusion rate.
the incidence tended to decrease with decreasing infusion rate in pigs with a PFO. However, a threshold value did not appear in this group, although such a threshold value (0.100 ml · kg\(^{-1}\) · min\(^{-1}\)) was observed in group C.

The bubbles emerging into the left atrium through a PFO (Fig. 1) demonstrated a higher intensity in the ultrasonic image than the air bubbles detected in the pigs without a PFO. This observation could indicate that the arterial bubbles were larger in the pigs with a PFO than in the control pigs (17). Furthermore, the number of bubbles that reached the systemic circulation seemed to be increased in group PFO compared to group C.

**Paradoxical air embolism in relation to hemodynamic changes**

The hemodynamic changes observed in control pigs after the infusion rates of 0.050, 0.100, and 0.200 ml · kg\(^{-1}\) · min\(^{-1}\) have been extensively described in previous papers (8, 9). The pigs of group PFO seemed to follow the same pressure profiles as those of group C. Thus, the air infusions were followed by an increase in mean pulmonary arterial pressure (PAP) and in mean right atrial pressure (RAP) and by a decrease in MAP. The three intravascular pressures stabilized after 5–20 min during all infusions at the two lowest rates, 0.050 and 0.075 ml · kg\(^{-1}\) · min\(^{-1}\) (Fig. 2A). In

![Fig. 2. Course in time of PAP (solid squares) and MAP (open squares) response in 3 pigs. Zero time is the start point of the air infusion. A, pig that received 0.05 ml · kg\(^{-1}\) · min\(^{-1}\) without any PAE; B, pig from group C that received 0.100 ml · kg\(^{-1}\) · min\(^{-1}\), with PAE; C, pig with a PFO that received 0.100 ml · kg\(^{-1}\) · min\(^{-1}\), with PAE. Arrows indicate the different points at which PAE occurred in the two latter pigs.](image-url)
contrast, the infusion rates of 0.100 and 0.200 were usually followed by a subsequent
decrease after the immediate rise in PAP (Fig. 2B). A steadily increasing RAP and a
decreasing MAP were observed as well. Some of the pigs that received air at the two
highest rates died before the 30-min infusion was finished, associated with a large
decrease in their MAP to values below 20 mmHg.

At PAE time, PAP and RAP were significantly increased in both group PFO_{RA} (P < 0.001 and P = 0.008, respectively) and group PFO_{RV} (P < 0.001 and P = 0.008, respectively) (Table 2), and MAP was significantly reduced compared to baseline values (P < 0.001 for both groups).

Thus, in pigs with a PFO, arterial bubbles were detected during the period when
the PAP increased. Furthermore, MAP, although significantly reduced from baseline,
was still 76% (group PFO_{RA}) and 67% (group PFO_{RV}) of the mean baseline value
(Fig. 2C). In contrast, control pigs showed arterial bubbles when PAP had returned
to baseline values after the immediate increase, and MAP was only 28% of mean
baseline value (Fig. 2B). PAP and MAP in the two PFO subgroups were therefore
significantly higher than the corresponding intravascular pressures in group C (Table
2). One should note, however, that the mean baseline MAP for group PFO_{RA} was
significantly lower than that for group C (P = 0.011).

Infused air volume

There was a negative correlation between infusion rate and time of detection of
arterial bubbles for group PFO_{RA}, group PFO_{RV}, and group C (Fig. 3). However, this
correlation was nonsignificant for the first group. Furthermore, the infused volume for
group PFO_{RA} (0.62 ± 0.34 ml · kg⁻¹, sd) and for group PFO_{RV} (0.73 ± 0.28 ml · kg⁻¹)
was significantly lower than that for group C (1.83 ± 0.64 ml · kg⁻¹, P < 0.001) (Fig. 4).
No significant difference was observed between the two PFO subgroups (P > 0.3).

Paradoxical air embolism in relation to size of the patent foramen ovale

The size of the PFOs as determined at autopsy was 4.5 ± 3.1 mm in diameter,
range 1.0–12.5 mm (Fig. 5, n = 17, one of the PFOs was not measured). The size of
the PFO was not related to the occurrence of PAE; there was no correlation between

| TABLE 2 |
|---|---|---|---|
| **Intravascular Pressures when PAE Occurred in Pigs with a PFO and in Control Pigs** |
| **Group** | **n** | **PAP, mmHg** | **MAP, mmHg** | **RAP, mmHg** |
| | | **Baseline** | **At PAE** | **Baseline** | **At PAE** | **Baseline** | **At PAE** |
| PFO_{RA} | 12 | 18 ± 4.0 | 31 ± 5.3 | 83 ± 9 | 63 ± 13 | 3.7 ± 1.6 | 4.6 ± 1.5 |
| PFO_{RV} | 12 | 16 ± 3.9 | 34 ± 4.8 | 94 ± 15 | 60 ± 18 | 3.3 ± 1.4 | 5.2 ± 1.9 |
| C | 9 | 18 ± 4.0 | 23 ± 8.0 | 101 ± 15 | 27 ± 6 | — | — |

*Values are means ± sd. *P < 0.05; †P < 0.01; compared to group C. n, no. of infusions with PAE. *n = 9.*
Fig. 3. Relationship between infusion rate and time of onset of PAE. $r$, Correlation coefficient (using Spearman's rank correlation). A, group PFO$_{RA}$ ($n = 12$ infusions with PAE); B, group PFO$_{RV}$ ($n = 12$ infusions with PAE); C, group C ($n = 9$ infusions with PAE).

Fig. 4. Infused air volumes at time of the PAE (i.e., the time at which PAE was observed) is demonstrated for group PFO$_{RA}$, for group PFO$_{RV}$, and for group C. Straight lines indicate mean values. $P < 0.001$ for both PFO groups when compared to the control group.

Injected air volume and size. Furthermore, no correlation was found between size of the PFO and either the increase in RAP or PAP or the decrease in MAP. Thus, in spite of possessing PFOs of 11 and 12.5 mm diameter, 3 of the pigs given right atrial infusions at the lowest rate, 0.050 ml·kg$^{-1}$·min$^{-1}$, did not develop arterial bubbles.
However, bubbles did appear in the left atrium of some of those pigs with a foramen of 1.0 mm diameter at the same infusion rate.

**DISCUSSION**

The present study has demonstrated that venous air bubbles were more likely to emerge into the left atrium through a PFO than via the pulmonary circulation in mechanically ventilated pigs. When arterial bubbles were detected, the hemodynamic changes were less dramatic in the pigs with a PFO than in the control pigs. Finally, a lesser volume of air was infused before arterial bubbles appeared in the former group compared to the latter. Previous studies have tried to investigate the phenomenon of PAE in dogs (5, 6), in sheep (7), and in pigs (4, 8, 9) either by studying the passage of gas bubbles through a surgically created, atrial septal defect (4) or through the pulmonary circulation (5–9). A comparison of animals with a naturally occurring atrial septal defect, namely a PFO, with animals without such a connection has to our knowledge not been reported previously.

**Incidence of paradoxical air embolism and hemodynamic changes**

The incidence of PAE seemed to be related to the air infusion rate in both group PFO and group C. In control pigs, no PAE occurred during infusion at the lowest rate, suggesting a threshold value for PAE appearance (8). We do not know if a threshold value also would appear in pigs with a PFO if infusion rates below 0.050 ml \cdot kg^{-1} \cdot min^{-1} were used. The hemodynamic effects during air infusion at lower rates might not be large enough to induce a shunt from the right to the left atrium. However, in 5% of humans, a right-to-left shunt exists during spontaneous breathing, without the use of a Valsalva maneuver to change the pressure gradient between the atria (18, 19). It is therefore possible that such a shunt can occur also in the pigs before air bubbles enter the pulmonary circulation and change the hemodynamics.

If no right-to-left shunt is present at baseline levels, there certainly have to be hemodynamic alterations during venous air embolism for air bubbles to emerge into the left atrium through a PFO. Our study revealed significant changes in PAP, MAP, and RAP at PAE time. Gas loading in the pulmonary circulation at these doses (≥ 0.050 ml \cdot kg^{-1} \cdot min^{-1}) will increase the PAP in pigs (8). Furthermore, increased PAP may induce a backward pressure resulting in an increased RAP. Finally, the
MAP decrease might be explained by a reduced blood flow or a reduced vascular resistance or both (20), variables that were not measured or calculated in our pigs.

Other experimental studies have tried to relate the occurrence of PAE to the gradient existing between the mean pressures in the atria, but Black et al. (4) did not succeed in demonstrating a positive gradient between the right and the left atrium when the mean pressures were compared at the time that arterial bubbles were detected. However, they did find that the RAP exceeded the left atrial pressure (LAP) during some stages of the heart cycle. In the present study, the RAP was significantly increased at PAE time, but LAP was not measured.

In another study of 6 pigs, we measured LAP during a 15-min infusion of 0.050 ml - kg \(^{-1}\) - min \(^{-1}\) (21). A left conventional thoracotomy was performed, with a catheter inserted directly into the left atrium. A decrease of 1–2 mmHg was observed in these pigs after 5 and 10 min infusions, followed by a stabilization during the final 5 min. In 1 pig a more dramatic MAP decrease was observed than in the other pigs, and the LAP fall was then even larger. Although the pigs in the present study had their chests closed during the experiments, we would not expect the direction of the change in LAP to be different from the change in LAP observed in pigs with open chests.

Our results show that PAE time tended to correlate inversely with the infusion rate. This can be explained by the fact that the rate of change in PAP and in MAP during air infusion is related to the rate of infusion (8), and that a change in PAP and MAP was necessary for a right-to-left shunt to occur in the pigs.

**Size of the patent foramen ovale**

In this study, 33% of the pigs had a PFO. Since the pigs were selected from several other studies, this incidence will only be approximate. The opening was usually valvelike, which is difficult to mimic when surgically creating an atrial septal defect (4). PFO has been demonstrated at autopsy in 20–34% of humans with no history of cardiac disease (22). Furthermore, the size of the opening in the pigs (mean: 4.5 mm, range 1.0–12.5 mm) did not differ much from those measured in humans [mean: 4.9 mm, range 1–19 mm (22)]. It has been suggested (18) that the size of the PFO may be important for the occurrence of PAE. However, we were not able to demonstrate any relationship between the size of the PFO and the incidence of PAE or the infused air volume. Nor did we find any relationship between the hemodynamic changes at PAE time and the size of the PFO. However, it is likely that a large opening in the atrial septum will permit more blood to reach the left atrium from the right atrium if a right-to-left shunt is present. Thus, more bubbles may reach the left side of the heart through a large opening than through a very narrow PFO, and the bubbles could thereby induce more serious symptoms in the arterial circulation in the former case than in the latter.

**Limitations of the study**

In clinical situations, venous bubbles usually reach the right atrium via the two caval veins. Thus, one objection to the results of our study may be the inclusion of results based on air infusions through a right ventricular catheter. The direction of blood flow in relation to the localization of the atrial septal defect has been suggested as one of the reasons why the gradient between the two mean atrial pressures is
insufficient to be critical for occurrence of PAE (4). However, in the present study the results obtained during right ventricular infusions were not significantly different from those obtained during atrial infusions. When arterial bubbles were detected there was a tendency for the hemodynamic changes to be larger in group PFO\textsubscript{rv} than in group PFO\textsubscript{ra}. This could be explained by the fact that a retrograde flow from the right ventricle into the right atrium was required before the air bubbles could reach the left atrium. In all pigs the increase in PAP during embolization probably increased this retrograde flow backward through the tricuspid valve and thereby also increased the RAP.

The rate of air bubbles delivered to the right atrium was much higher during atrial infusions than during ventricular infusions because most of the bubbles entered the pulmonary artery during the ventricular infusions. This study shows that the rate of this delivery to the right atrium probably was not very important because there was no significant difference between the 2 groups when infused volume was compared. It was the gas bubbles that entered the pulmonary circulation and induced an increase in PAP that probably determined the RAP/LAP gradient and thereby any PAE.

Furthermore, pigs in the control group all had a right ventricular catheter because the study was initially designed to investigate transpulmonary passage. It is unlikely that the positioning of the catheter could have influenced either the incidence or the time of PAE appearance in these pigs. This is because the time it takes for bubbles infused into the right atrium to reach the right ventricle is negligible, and eventually it is the gas loading in the pulmonary circulation that determines any transpulmonary passage in control pigs.

Another limitation to the study is the use of pigs that received Pluronic. The surfactant did not seem to alter transpulmonary passage of bubbles or the hemodynamic variables measured in the present study. Also, the diameter of the PFOs will be larger than the diameter of most of the bubbles. It is therefore unlikely that Pluronic would influence the shunt or the transport of bubbles between the two atria.

Finally, one should note that MAP at the baseline level was significantly lower in group PFO\textsubscript{ra} than in group C. This could be because some of the former pigs had received several infusions and the recovery time (≥ 20 min) was inadequate, whereas the pigs in group C only received one infusion. Since the results of group PFO\textsubscript{ra} did not differ from those of group PFO\textsubscript{rv}, this difference in experimental protocol did not seem to be of importance for the conclusion in this study.

Clinical implications

As we have also demonstrated in previous studies, it was difficult to break down the lung filter of mechanically ventilated pigs by either overloading (8) or by use of a pulmonary vasodilator (9). The spillover of bubbles into the arterial circulation seemed to be an almost preterminal event, in contrast to what was observed in pigs with a PFO. This difference was also reflected in the larger volume of air infused in the control pigs at PAE time, compared to the volume infused in the PFO pigs. Thus, if the pigs without a PFO were able to maintain a MAP above 40–50 mmHg, no arterial bubbles could be detected. Other studies have shown that this is not the case with dogs (5, 6) or sheep (7). Although caution is required when extrapolating experimental findings, if our model provides a reasonable prediction for humans, the
20–34% of the population who have a PFO will be at greater risk of developing PAE when venous air bubbles are present.

In surgical procedures in which the incidence of venous air embolism is high, e.g., neurosurgery in the sitting position (3), some patients have lately been investigated before treatment, using preoperative echocardiography to detect any PFO, after contrast injection and Valsalva maneuver. Black et al. (23), however, concluded that the advantage of this at present was not worth the added expense because the incidence of false-negative results from such examinations was too high. Intraoperative transesophageal echocardiography was suggested as being a better choice because it can be used to detect a PFO, venous air embolism, or bubbles in the left heart during the operation (24, 25).

The studies of Moon et al. (14) and Wilmhurst et al. (15) in divers with a history of decompression sickness have focused on the importance of PFO as the pathway for venous bubbles into the arterial circulation, and eventually into the cerebral circulation. Our results could lend support to their conclusions that the existence of a PFO enhances the risk of PAE. However, it is important to emphasize that our pigs were ventilated with a respirator, using intermittent positive pressure ventilation (IPPV). This condition will not be directly comparable to the divers’ situation because they are breathing spontaneously during decompression. IPPV can alter hemodynamics such as the right atrial pressure and the pulmonary blood flow (26). Likewise, the two highest infusion rates used in our study are probably considerably higher than those experienced by divers. Finally, it was not possible to estimate the size of the venous bubbles introduced, because this depends on the flow rate at the infusion site as well as on mixing in the right ventricle (16). The measured size of the venous bubbles in dogs after decompression was 19–700 μm (27). It is likely that the size of the present bubbles in our infusions lay in the upper part of this range, and some may have been even larger.

Our results showed a delay before PAE occurred, which indicates that no right-to-left shunt was present at baseline. However, as mentioned previously in this discussion, in about 5% of human control subjects a shunt has been revealed by spontaneous breathing without increasing the intrathoracic pressure by a Valsalva maneuver (18, 19). In these individuals, bubbles emerge into the left atrium immediately after appearance in the right atrium because there is already a right-to-left shunt, at least during some stages of the heart cycle. Both the study by Moon et al. (14) and that by Wilmhurst et al. (15) demonstrated that divers with such a shunt show an even greater susceptibility to developing some form of decompression sickness. It is possible that we could have detected a right-to-left shunt at baseline in some pigs if we had increased the number of pigs with a PFO. It is likely that such a shunt could be detected only during right atrial infusions, because the right ventricular infusions probably were dependent on a small increase in the PAP for bubbles to flow retrograde to the right atrium. Finally, the pressure gradient between the atria in mechanically ventilated pigs may differ from that in spontaneously breathing pigs, and the two pig models may therefore give different results.

Thus, we conclude that, in mechanically ventilated pigs, venous air bubbles are more likely to emerge into the left atrium through a PFO than via the pulmonary circulation. When arterial bubbles were detected, the PAP, MAP, and RAP were significantly changed from baseline values. The hemodynamic changes were, however, less dramatic in the pigs with a PFO than in the control pigs. Finally, the volume of air infused before PAE occurred was less in the former pigs compared to the latter.
AIR EMBOLISM AND PATENT FORAMEN OVALE

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