Arterial gas bubbles after decompression in pigs with patent foramen ovale

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Vik A, Jenssen BM, Brubakk A.-O. Arterial gas bubbles after decompression in pigs with patent foramen ovale. Undersea & Hyperbaric Med 1993; 20(2):121–132.—With patent foramen ovale (PFO), thought to be a risk factor for some forms of DCS, venous bubbles may pass through the patent opening to become arterial bubbles. We exposed 14 anesthetized, spontaneously breathing pigs to air at 5 bar (500 kPa, absolute pressure) for 30 min and then rapidly decompressed at 2 bar/min to 1 bar. We measured intravascular pressures, blood gases, and, with transesophageal echocardiography, bubbles in the pulmonary artery and ascending aorta. Autopsy showed that six of the pigs had a PFO. Arterial bubbles occurred more frequently in the PFO group (in six out of six) than in the non-PFO group (in two out of eight, \( P < 0.01 \)). When arterial bubbles were detected, the venous bubble count and the pulmonary artery pressure tended to be lower in pigs with PFO than in pigs without a PFO. We conclude that a PFO increases the risk of arterial bubbles after decompression.

decompression sickness, right-to-left shunt, air embolism, spillover, congenital heart defect, patent foramen ovale

Arterial gas bubbles have been detected in divers after decompression (1), and they may be involved in DCS (2). Except during barotrauma of the lungs (3), these arterial gas bubbles are assumed to arise on the venous side of the circulation (4). Venous gas bubbles may enter the arterial circulation as a result of either transpulmonary passage (5, 6) or passage through a patent foramen ovale (PFO) (7, 8). Such arterial bubbles are termed paradoxical gas emboli.

Recent studies have indicated that the risk of some forms of DCS is increased in divers with a PFO (9, 10), and it is therefore possible that venous gas bubbles that arise during and after decompression are more likely to traverse a PFO than to travel through the pulmonary vasculature into the arterial circulation. This assumption is supported by the results of an experimental study in pigs; during air infusion we found an increased incidence of arterial gas bubbles in pigs with a PFO compared to pigs without a PFO (11). To our knowledge, no decompression study has investigated passage of venous gas bubbles through a PFO into the arterial circulation.
The aim of the present study was to test the hypothesis that after rapid decompression, pigs with a PFO are more likely to have arterial bubbles than pigs without a PFO. Since we have developed a pig model that allows estimation of relative quantities of gas bubbles in the venous circulation after decompression, using two-dimensional imaging of the pulmonary artery, the occurrence of arterial gas bubbles could be related to the degree of venous gas loading.

MATERIALS AND METHODS

Surgical procedures

Fourteen domestic farm swine (2–3 mo. old, body weight 19.5–29.0 kg) were used as experimental animals. The pigs were fasted for 16 h with free access to water. Fifteen to twenty minutes before induction of anesthesia, the pigs received premedication: 7–9 mg/kg azaperonum (Stresnils, Janssen) was injected intramuscularly; atropinsulfate (1 mg, Atropin, Hydro Pharma) was thereafter given intravenously via an ear vein. Anesthesia was induced by thiopental sodium (5 mg/kg, Thiopenton Natrium, Nycom Pharma) and ketamine (20 mg/kg, Ketalar, Parke Davis) and maintained by a continuous i.v. infusion of ketamine in 0.9% NaCl (30 mg·kg$^{-1}$·h$^{-1}$). A tracheotomy was performed, after which the pigs were breathing spontaneously through an endotracheal tube, in the supine position. During surgery, body temperature was monitored by a rectal probe and maintained at 37.5°–38.5°C using a heating pad. During the dive, the temperature inside the chamber was also regulated (29.5°–30.5°C). Because a superficial, irregular respiratory pattern was observed approximately 30 min after anesthesia was induced, a bolus dose of α-chloralose in 0.9% NaCl (10–15 mg/kg, 0.25% solution, Sigma, St. Louis, MO) was injected i.v. One or two supplemental doses were usually injected during the following 30 min to achieve a more regular respiratory rate. After injection of the α-chloralose solution, the ketamine infusion provided the pigs with i.v. fluid at a rate of approximately 3–4 ml·kg$^{-1}$·h$^{-1}$.

Two polyethylene catheters (0.76 mm i.d.) were introduced into the left jugular vein and moved into the pulmonary artery to measure pulmonary arterial pressure and to obtain mixed venous blood samples for gas analysis. The third catheter was positioned in the right atrium via the right jugular vein for measurement of right atrial pressure. Two polyethylene catheters (1.14 and 0.76 mm i.d.) were inserted into the right femoral artery and advanced into the abdominal aorta for continuous monitoring of arterial pressure and to obtain samples for analysis of blood-gas composition. All intravascular pressures were recorded on a Grass polygraph (model 7D, Grass Instrument Co., Quincy, MA) using transducers (Sorensen Transcap II, Abbott Laboratories) that were calibrated against a mercury manometer, with zero pressure referred to the left ventricular mid-level. Calculations of mean pulmonary arterial pressure (PAP), mean right arterial pressure (RAP), and mean arterial pressure (MAP) in millimeters of mercury were made after the experiments. Arterial blood gases (P$_{A,O_2}$ and P$_{A,CO_2}$) in kilopascals were measured on an IL-1306 pH–blood gas analyzer (Instrumentation Laboratories).
 Bubble detection

A transesophageal echocardiographic (TEE) transducer (6.5 MHz), interfaced with a color-flow ultrasonic scanner (CFM 750, Vingmed A/S, Horten, Norway), was inserted and positioned to obtain a simultaneous two-dimensional view of the pulmonary artery and the aorta. If arterial bubbles occurred, it was possible to change the position of the transducer to provide an image of the pulmonary artery, the right atrium, and the left atrium. Ultrasound images were stored on videotape during compression and decompression periods, as well as during the following 90 min. Venous and arterial gas bubbles could be counted automatically after transmission of digitized images from the CFM scanner to a Macintosh computer, or the bubbles could be counted manually from the stored images (12).

Experimental procedure

After surgery was finished, the pigs were placed inside a chamber (300 liter), specially constructed to fit pigs of this size. At least 30 min were needed for stabilization, and the predive data used in the present study were collected 3–5 min before compression started.

Fourteen pigs underwent a 30-min exposure to 5 bar (500 kPa, absolute pressure; compression rate 2 bar/min) followed by a rapid decompression to 1 bar (2 bar/min). Bottom time was calculated from the beginning of compression to the beginning of decompression. The pigs were breathing chamber air during the dive, and soda lime was placed inside the chamber to prevent an increase of CO₂ in the chamber atmosphere. Monitoring of bubble formation and intravascular pressures was done during the dive using special chamber connectors, and after decompression monitoring continued, with the final measurement made after 90 min.

After the dive experiments, the hearts of all the pigs were investigated at autopsy; six pigs were found to have a patent foramen ovale (1.8–5.0 mm diameter) and made up the PFO group [body weight 23.6 kg (± 2.9)], whereas the other eight had no PFO and served as controls [the non-PFO group, body weight 22.8 kg (± 2.0)]. The results concerning venous bubble formation and relationship to hemodynamic responses in the non-PFO group will be published separately.

Statistics

Fisher’s exact test (one-tailed) was used to test whether the incidence of arterial gas bubbles was higher in the PFO group than in the non-PFO group. Maximum values of venous bubble count were tested for any difference between the groups by the unpaired Student’s t test. Predive values and the maximum or minimum values of intravascular pressures and blood gases in the two groups were compared using a two-way analysis of variance and the Student’s t test, with Bonferroni correction for multiple comparisons. For the PFO group, paired Student’s t test was used to test if each variable had changed significantly from the predive values when the first
arterial gas bubbles were detected. Most values are cited as means (SD), although individual observational values are presented separately for the non-PFO group.

RESULTS

Venous gas bubbles

We observed gas bubbles in the pulmonary artery in all pigs in both the PFO and non-PFO groups. Venous bubbles appeared immediately after the surface was reached or even 10–15 s before (at approximately 1.5 bar) and they increased in number to reach a maximum between 5 and 30 min afterward. The maximum bubble count in the PFO group [200 bubbles $\cdot$ s$^{-1}$ $\cdot$ cm$^{-2}$ (SD 152)] did not differ significantly from that of the non-PFO group [221 bubbles $\cdot$ s$^{-1}$ $\cdot$ cm$^{-2}$ (SD 107), $P = 0.77$] (Fig. 1). Ninety minutes after the decompression, bubbles were still present in the pulmonary artery in all pigs (one pig in the PFO group died 35 min after decompression).

Arterial gas bubbles

Arterial gas bubbles appeared in all six of the pigs with a PFO and in only two of eight pigs that had no PFO (Fig. 2 and Table 1). The difference between the groups was significant, $P = 0.009$). The bubbles were detected in both groups in the ascending aorta during the initial 15 min after surfacing. In one PFO pig we detected arterial bubbles 4 min after decompression. Due to technical problems we do not know if this pig had arterial bubbles immediately on reaching the surface. In both groups the number of arterial bubbles increased until a peak was reached between 15 and 30 min after decompression, whereafter the bubble count decreased again. For both groups the count of arterial bubbles seemed to follow the same time course as the count of venous gas bubbles (Fig. 3). When arterial bubbles were detected, the venous bubble count seemed to be lower in the PFO group than in the non-PFO group (Table 2). Sixty minutes after decompression, solitary arterial bubbles were observed occasionally in the PFO group; none was observed in any pig without a PFO.

FIG. 1—Maximum bubble count (bubbles $\cdot$ s$^{-1}$ $\cdot$ cm$^{-2}$) of six pigs in the PFO group and seven pigs in the non-PFO group. (In the eighth pig in the non-PFO group, the quality of the ultrasound image was reduced and permitted no accurate counting to be done.)
Table 1: Incidence and Time of Detection of Arterial Gas Bubbles in Pigs with PFO and in Pigs Without a PFO

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Incidence</th>
<th>Time, a min</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFO</td>
<td>6</td>
<td>6/64 (100%)</td>
<td>&lt;4', 7, 8, 10, 13, 15</td>
</tr>
<tr>
<td>Non-PFO</td>
<td>8</td>
<td>2/8 (25%)</td>
<td>10, 12</td>
</tr>
</tbody>
</table>

*aMinutes after decompression; *bP = 0.009 compared to the incidence in the non-PFO group; *cexact time for the occurrence of arterial gas bubbles is not available (see text).

Hemodynamic changes

The PAP, RAP, and MAP values for both groups formed a peaked curve after surfacing (Fig. 4). When arterial gas bubbles were detected in the PFO group, both PAP and MAP values had increased significantly from the predive values (Table 2). In the two pigs without a PFO that had arterial gas bubbles, the same variables had also increased at time of detection of arterial bubbles. At that time, the increase in PAP seemed to be much greater in the non-PFO group than in the PFO group.

When the predive and maximum values of PAP, RAP, and MAP from PFO pigs were compared with data from pigs without a PFO, there were no significant differences (Table 3). Similarly, there was no difference between predive values or minimum values of the PaO₂, or between predive PaCO₂ values for PFO pigs and pigs without PFO. No change in the PaCO₂ was observed after decompression in any of the groups.

One pig in the PFO group died 35 min after decompression. No increase in MAP was observed in this pig after surfacing, in direct contrast to the increase observed in all the other pigs in both groups.
FIG. 3—Time course of development of venous and arterial gas bubbles in one of the pigs in the PFO group (closed circles, solid line) and in one of the pigs in the non-PFO group (open circles, dotted line). (Venous bubble count is given as bubbles per second per square centimeter, whereas the arterial bubble count is bubbles per second in the aorta.)

Table 2: Venous Bubble Count and Hemodynamic Variables at the Time When Arterial Gas Bubbles Were Detected

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Point of Time</th>
<th>Venous Bubble Count, bubbles $\cdot$ s$^{-1}$ $\cdot$ cm$^{-2}$</th>
<th>PAP, mmHg</th>
<th>RAP, mmHg</th>
<th>MAP, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFO</td>
<td>5</td>
<td>predive</td>
<td>15 (1)</td>
<td>2.4 (1.5)</td>
<td>83 (12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>arterial bubbles$^a$</td>
<td>45 (41)</td>
<td>20 (3)</td>
<td>2.7 (1.2)</td>
<td>90 (15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$P$ values</td>
<td>0.005</td>
<td>0.242</td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>#6$^b$</td>
<td></td>
<td>predive</td>
<td>20</td>
<td>1.5</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>arterial bubbles$^a$</td>
<td>$\leq$ 21</td>
<td>1.5</td>
<td>$\leq$ 81</td>
<td></td>
</tr>
<tr>
<td>Non-PFO</td>
<td>2</td>
<td>predive</td>
<td>11, 13</td>
<td>1.5, 3.0</td>
<td>80, 88</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>arterial bubbles$^a$</td>
<td>155, 170</td>
<td>2.0, 4.0</td>
<td>94, 104</td>
<td></td>
</tr>
</tbody>
</table>

$^a$Data obtained at the time when arterial gas bubbles were first detected. $^b$The sixth pig is not included in the statistical evaluation (see text), and venous bubble count was not available at time of detection of arterial bubbles. $P$ values are for the comparison of hemodynamic variables before the dive and when arterial gas bubbles were detected. Values are means (SD) in the PFO group; values for individual observations are shown for the non-PFO group.
DISCUSSION

The present study in pigs shows that after decompression, gas bubbles in the arterial circulation were more likely to have passed through a PFO than to have followed a transpulmonary route. This statement is based on the finding of a higher incidence of arterial gas bubbles in pigs with a PFO than in pigs without a PFO. Furthermore, the results suggest a tendency for arterial gas bubbles to occur at lower venous bubble count and lower PAP values in the PFO group than in the non-PFO group. These findings indicate that arterial bubbles appeared at a lower loading of venous gas bubbles in the PFO pigs than in the pigs without a PFO (13–15). It should be mentioned, however, that only two pigs in the non-PFO group were found to show arterial bubbles.
Table 3: Maximum or Minimum Values of Hemodynamic Variables and Blood Gases After Decompression

<table>
<thead>
<tr>
<th></th>
<th>PAP</th>
<th>RAP</th>
<th>MAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmHg</td>
<td>mmHg</td>
<td>mmHg</td>
</tr>
<tr>
<td>Predive</td>
<td>Max</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predive</td>
<td>Max</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFO</td>
<td>6</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Non-PFO</td>
<td>8</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

P < 0.05

"No significant difference was observed between the two groups. Values are means (SD)."

\[ \text{P}_{\text{CO}_2} \]

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Inasmuch as there was no difference between maximum values of venous bubble count in the two groups, we can assume that a similar amount of gas appeared as venous bubbles in the PFO group and the non-PFO group. This assumption is supported by the fact that the maximum change in intravascular pressures and blood gases did not differ between the groups (13–15). Thus, our results cannot be explained by a higher venous gas loading or a different ventilation in the PFO pigs compared to that of the pigs without a PFO.

The occurrence of arterial gas bubbles has been investigated in decompression studies on other animal species (16–19). In three of these four studies, venous gas bubbles seemed to arise before any gas bubbles were detected in the arterial circulation (17–19). However, conclusions about transpulmonary passage were drawn without any account being taken of the fact that bubbles might have emerged through a PFO.

We detected arterial gas bubbles in all pigs with a PFO, and we therefore assume that the gas bubbles had passed through the PFO. Since the occurrence of arterial gas bubbles seemed to follow the same time course as the venous bubble count, it is unlikely that arterial gas bubbles appeared as a result of barotrauma of the lung during rapid decompression. Immediately after surfacing we detected venous gas bubbles but no arterial bubbles in five of the pigs in the PFO group. This finding indicates that no right-to-left shunt was present when the surface was reached (20).

Inasmuch as the PAP values had changed significantly from pre-dive values when arterial bubbles were detected, an increase in PAP was probably necessary before a right-to-left shunt could occur (21). This suggestion accords with our results from a previous study (11) using air infusion in mechanically ventilated pigs with a PFO, where we also observed an increase in PAP at the time arterial bubbles were detected.

The sixth pig in the PFO group had arterial bubbles <4 min after surfacing, and almost no changes in PAP and MAP and no change in RAP were observed. We can only speculate on the possibility that this pig had a right-to-left shunt before any gas emboli entered the pulmonary circulation. Such a shunt, that is not dependent on a Valsalva maneuver or other factors to change the pressure gradient between the atria, does appear in 5–6% of humans (22, 23).

Another pig in the PFO group died 35 min after surfacing; in contrast, all pigs in the control group survived. We do not know whether arterial gas bubbles were the cause of this death, although an increased mortality was observed in decompressed hamsters that had gas bubbles in the arterial circulation (19). Arterial hypotension was observed only a few minutes after the first bubbles were detected in the ascending aorta, but the number of arterial bubbles recorded in this pig did not seem to be higher than the number in the other five pigs. It is possible that lower MAP values pre-dive (74 mmHg before compression), compared to those observed in most of the other pigs, contributed to the cardiopulmonary collapse.

Gas bubbles in the ascending aorta were also detected in two of the eight pigs without a PFO. Although formation of gas bubbles in the arterial circulation by de novo nucleation is theoretically possible, it is generally accepted that, except during barotrauma, arterial gas bubbles arise on the venous side of the circulation (4). Thus, the arterial bubbles most likely followed a transpulmonary route. The bubbles were first observed in the aorta when the count of venous gas bubbles was high (Table 2) and the PAP values had increased approximately 100% compared to the baseline values. During air infusion in mechanically ventilated pigs without a PFO (15), we
also detected arterial bubbles when the gas loading was high. However, arterial bubbles only appeared after a circulatory collapse, which indicated a very resistant lung filter. During and after decompression, the venous gas bubbles are probably smaller (4–700 µm) (24, 25) than during air infusion (26). We therefore suggest that it was some of the smaller-sized bubbles that escaped pulmonary filtration after decompression in two of the pigs without a PFO (27).

We obtained our results from an animal model involving severe decompression stress on anesthetized pigs; furthermore, the number of pigs used in the study was low. Caution is therefore called for when extrapolating the results to humans. However, it has been suggested that arterial gas bubbles are involved in DCS (2), and our results may help to understand the increased risk of DCS observed in divers with a PFO (9, 10). It is, however, important to be aware of a recent study by Cross et al. (28) in which a PFO was detected in 31% of divers who never experienced DCS. This incidence is close to that found at autopsy in humans (29). Their results show that in divers, the presence of a PFO alone is insufficient to induce symptoms of the disease. It is important to keep in mind that the passage of gas bubbles through a PFO is always dependent on the venous gas loading and thereby on the decompression profile. Thus, in five of our six pigs with a PFO, we observed arterial gas bubbles when the amount of gas that appeared as bubbles in the pulmonary circulation was sufficiently high to have induced an increase in the PAP. Furthermore, in a previous study on pigs that received an air infusion (11), we observed that the risk of arterial gas bubbles seemed to decrease with a decrease in the infusion rate.

It is often assumed that arterial gas emboli that appear in divers during the initial 5–15 min after decompression occur as a result of barotrauma of the lung (3). In such cases, clinical and radiologic evidence of lung pathology is rare (3). We therefore speculate on the possibility that venous gas bubbles have entered the arterial circulation through a PFO in some of those cases of arterial gas embolism.

In conclusion, this study has demonstrated that after a rapid decompression in pigs, the pigs with a PFO were more likely to have arterial gas bubbles than pigs without a PFO. The results may explain some of the mechanisms behind the findings of an increased risk of DCS in divers with a PFO.

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REFERENCES


