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Effects of treatment with Pluronic F-68 during continuous venous air embolism in swine

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Jenssen BM, Vik A, Brubakk A.O. Effects of treatment with Pluronic F-68 during continuous venous air embolism in swine. Undersea & Hyperbaric Med 1993; 20(1):17–26.—Treatment with the surface-active agent Pluronic F-68, shown to modulate the hemodynamic effects of venous air emboli (VAE) in dogs, may be useful for treatment of VAE in divers. We report on the effects of injections of Pluronic F-68 on responses to continuous air infusion in swine. Pretreatment made no significant difference in any hemodynamic or ventilatory variables, but the rise of pulmonary vascular resistance caused by air infusion was greater in surfactant-treated animals; this was also evident after a second treatment during the air infusion. The small effect of surfactant treatment in our study on swine contrasts the effects reported previously in dogs, and could be due to species-specific differences in lung physiology–anatomy, or due to difference in experimental design. We speculate that the minor changes we observed were caused by deeper penetration of the bubbles into the pulmonary arterial tree after surfactant treatment.

venous air embolism, hemodynamic, respiration, ventilation, effects, swine

Venous air emboli (VAE) that may be formed during decompression are trapped in pulmonary arterioles (1, 2) and may cause elevated pulmonary arterial pressure (PAP) and increased pulmonary vascular resistance (PVR) (3, 4). The surface-active agent Pluronic F-68 has been demonstrated to modulate the hemodynamic effects of VAE in dogs, and treatment with Pluronic F-68 has been suggested to be advantageous for surgical patients when an increased risk of VAE exists (5). Pluronic F-68 could therefore also be considered as a treatment in divers who experience venous gas bubbles.

We investigated whether Pluronic F-68 modulates the effects of continuous air embolism (VAE) on pulmonary hemodynamics, pulmonary gas exchange, alveolar ventilation ($\dot{V}_A$), and alveolar ventilation: perfusion ratio ($\dot{V}_A:\dot{Q}$) in swine. The study also aims at examining whether the threshold for transpulmonary passage of VAE is reduced after pretreatment with Pluronic F-68, as has been suggested by others (6).

MATERIALS AND METHODS

Surgical and anesthetic procedures

Eleven domestic farm swine of either sex (age ~ 3 mo.) were randomly divided into a control group (C) [body weight (BW) = 20.7 kg, SD = 0.7, n = 5], and a Pluronic F-68 treated group (P) (BW = 21.3 kg, SD = 1.7, n = 6). All pigs were fasted for 16 h with access to water ad libitum. Fifteen to twenty minutes before anesthesia the animals received premedication: 7–9 mg · kg^{-1} azaperone (Sedaperone, Janssen) intramuscularly. Anesthesia was initiated with pentobarbital sodium (25–35 mg · kg^{-1}) via an ear vein and maintained with a 5–15 mg · kg^{-1} · h^{-1} continuous i.v. infusion. The pigs were tracheotomized and ventilated using a volume-regulated ventilator (model 613, Harvards Apparatus, South Nattick, MA) at a tidal volume of 7–12 ml · kg^{-1}. The respiratory rate, 10–20 breaths/min, was chosen to maintain an initial P_{CO_2} of between 30 and 35 mmHg. The tidal volume and respiratory rate were held constant throughout the experiment. The content of oxygen in the inspired air was determined before each experiment using an oxygen analyzer (S3 A, Applied Electrochemistry) and was 30.5% (SD = 0.31, n = 5) and 30.7% (SD = 1.7, n = 6) for the control and the Pluronic F-68-treated group, respectively. The urinary bladder was drained through a cystostomy. Rectal temperature was measured by means of a digital thermometer (Exacon MC 8700) and kept at 37.5°–38.5°C, which is within the normal range (7), by using a heating pad and wrappings.

Blood pressures

A polyethylene catheter (0.76 mm i.d.) was introduced into the right femoral artery and the tip moved into the abdominal aorta for measurements of systemic arterial pressure (MAP) and to obtain arterial blood for gas analysis. Another catheter was placed in the femoral vein for continuous infusion of fluid (0.9% NaCl). The catheter used for air infusion was placed via one jugular vein into the right ventricle. A second and third catheter were placed via the other jugular vein into the right atrium for measurement of central venous pressure (CVP) and into the pulmonary artery for measurements of PAP and to obtain mixed venous blood for gas analyses, respectively. The locations of all catheters were verified by connection to a pressure transducer. All blood pressures were measured by connecting the catheters to calibrated pressure transducers (Statham P23 ID), with zero pressure referring to the left ventricular mid level, and continually recorded on a pen recorder. All blood pressures are presented as mean pressures.

Respiratory and ventilatory variables

Blood samples were analyzed for P_{O_2} and P_{CO_2} using a 1306 blood gas analyzer (Instrumentation Laboratory). Content of oxygen in arterial and mixed venous blood [Ca_{O_2} and $C\bar{v}_{O_2}$ (ml/100 ml), respectively] was estimated using the relationship between P_{O_2} and C_{O_2} in pig blood (8). Since we are not aware of any reports of the relationship between P_{CO_2} and carbon dioxide content (C_{CO_2}) in pig blood, C_{CO_2} in arterial and mixed venous blood was estimated using the relationship between P_{CO_2} and C_{CO_2} in human blood (9).

Estimates of pulmonary blood flow ($\dot{Q}$, ml · kg^{-1} · min^{-1}) were made using the direct Fick method:

$$\dot{Q} = \frac{\dot{V}O_2}{Ca_{O_2} - C\bar{v}_{O_2}} \quad (1)$$

where $\dot{V}O_2$ is the oxygen consumption (ml O_2 · kg^{-1} · min^{-1}) calculated according to *Eq. 10*:

$$\dot{V}O_2 = \dot{V}E \cdot \frac{FI_{O_2} - FE_{O_2}}{[1 - (1 - RQ) \cdot FI_{O_2}] \cdot BW} \quad (2)$$

$\dot{V}E$ is expiratory ventilation (ml · min^{-1}, STPD) measured with a gas flow meter. FI_{O_2} and FE_{O_2} are the O_2 fractions of the inspiratory and expiratory air, respectively, and RQ is the respiratory quotient which was estimated from arteriovenous differences of Co_2 and Cco_2. BW is the body weight (kg) of the animal. The gas was analyzed by sampling a fraction of the respiratory gas, drying it using Silica gel, and passing it into an oxygen analyzer (S3A, Applied Electrochemistry). The FI_{O_2} was analyzed before the experiment and kept constant during the entire experiment, whereas gas for determination of FE_{O_2} was sampled after mixing in a 4-liter bottle. FE_{O_2} was determined continuously during the experiment and recorded on a chart writer (Watanabe Servocorder, SR 6310).

The carbon dioxide elimination ($\dot{V}CO_2$, ml CO_2 · kg^{-1} · min^{-1}) was calculated according to the equation:

$$\dot{V}CO_2 = \dot{V}E \cdot (FE_{CO_2} - FI_{CO_2}) \quad (3)$$

where the fraction of CO_2 was analyzed using a Leybold-Heraus CO_2 analyzer. The FI_{CO_2} was determined before the experiments and kept constant during the experiment, whereas FE_{CO_2} was analyzed continuously during the experiment by passing a dry fraction of the expired gas into the CO_2 analyzer and recording the output signal on a recorder (Graphtech Multicorder).

The physiologic (or effective) dead space ventilation ($\dot{V}D$, ml · kg^{-1} · min^{-1}) was calculated according to the equation:

$$\dot{V}D = \dot{V}E \cdot \frac{Pa_{CO_2} - PE_{CO_2}}{Pa_{CO_2} - PI_{CO_2}} \quad (4)$$

where $\dot{V}D$ is physiologic dead space ventilation in milliliters; PI_{CO_2} is inspired CO_2 pressure in mmHg, PE_{CO_2} is mixed expiratory CO_2 pressure in mmHg; $\dot{V}E$ is expiratory ventilation (11).

The effective alveolar ventilation (ventilation of blood perfused lung regions), $\dot{V}A$ (ml · kg^{-1} · min^{-1}), is equal to the difference between the total ventilation ($\dot{V}E$) and the effective deadspace ventilation:

$$\dot{V}A = \dot{V}E - \dot{V}D \quad (5)$$

Physiologic shunt fraction and vascular resistances

The total pulmonary shunt fraction was calculated using the equation:

$$\dot{Q}_{sp}/\dot{Q}_t = \frac{Cc_{O_2} - Ca_{O_2}}{Cc_{O_2} - C\bar{v}_{O_2}} \quad (6)$$

where $\dot{Q}_{sp}$ is shunt flow and $\dot{Q}_t$ is total flow through the pulmonary system. To estimate C_{CO_2} (end-capillary oxygen concentration, ml · liter^{-1}) it was assumed that the gas tension of end-capillary blood (P_{CO_2}) equaled the alveolar tension of O_2 ($P_{A_{O_2}}$). $P_{A_{O_2}}$ was calculated according to the equation:

$$P_{A_{O_2}} = P_{I_{O_2}} - \frac{P_{A_{CO_2}}}{RQ} \quad (7)$$

where $P_{I_{O_2}}$ (mmHg) is the inspired tension of oxygen, and $P_{A_{CO_2}}$ is the alveolar tension of CO_2 that is assumed to be equal to $P_{a_{CO_2}}$.

In estimating the total PVR (mmHg · ml^{-1} · min^{-1} · kg^{-1}), left arterial pressure was assumed to be zero, thus:

$$PVR = PAP / \dot{Q} \quad (8)$$

Systemic vascular resistance (SVR) was estimated as:

$$SVR = MAP - CVP / \dot{Q} \quad (9)$$

where MAP is mean arterial pressure (mmHg) and CVP is central venous pressure (mmHg).

Detection of arterial bubbles

To determine the possible transport of venous air bubbles into the systemic circulation, a 7.5 MHz transesophageal echocardiographic probe connected to a CFM 700 (Vingmed A/S, Horten, Norway) was inserted 30–40 cm into the esophagus and positioned to give a simultaneous two-dimensional image of the right pulmonary artery and the left atrium. By withdrawing the transducer by 1–2 cm, a view of the aorta and the main pulmonary artery was obtained. Bubbles were seen as high-intensity spots in the blood (4). The ultrasound image was continually videotaped during the experiments.

Experimental protocol

After the surgical intervention and placement of all catheters, all animals were allowed a stabilization period of at least 30 min. Six pigs were then given an i.v. dose of 1 ml · kg^{-1} of a 5% Pluronic F-68 solution, whereas the other five pigs received an identical i.v. dose of 0.9% NaCl. To allow the preparation to stabilize, baseline data from both groups were collected 20 min later. Five minutes later, the animals were given a continuous infusion of 0.05 ml air · kg^{-1} · min^{-1} into the right ventricle. A new set of data from both experimental groups was collected after 15 min of exposure to continuous VAE, which is 40 min after the animals received the Pluronic or sham infusion of saline.

To study whether Pluronic F-68 modifies the effects of VAE if given during continuous VAE, the Pluronic F-68 pretreated group received a second dose of 1 ml · kg^{-1} Pluronic F-68 1 h after start of embolization (while still receiving VAE at the same dose). The control group received an identical i.v. dose of 0.9% NaCl. Five minutes before the second treatment, baseline data were collected. Data were collected 15 min after the second treatment. The two different types of surfactant treatment are

chosen because in addition to pretreatment we wanted to elucidate the effects of treatment during a situation of continuous air embolism. Additional surfactant treatment during a situation of continuous air embolization will further clarify the effects on bubble formation. At the end of the experiment a postmortem examination of the heart was carried out to ensure that the animals included in this study did not have any intracardial shunts, such as a patent foramen ovale or a ductus arteriosus.

To test effects of VAE in the two groups, baseline values were compared with those obtained after the animals had received VAE for 15 min using paired Student's *t* test (Macintosh IIfx, StatWorks version 1.2, Cricket Software Inc., Philadelphia, PA). A probability of less than 0.05 was defined as significant. Values obtained in the two experimental groups were compared using Student's *t* test and the Bonferroni method. Since two comparisons were of interest, a *P* value of $0.05/2 = 0.025$ was defined as significant (12). All data are given as mean values ± SD.

RESULTS

Pretreatment

Baseline physiologic data after surfactant treatment (but before air infusion) and data obtained after 15 min of venous air infusion are listed in Table 1. After the first treatment with saline or Pluronic F-68, there were no statistical differences in the physiologic variables between the two groups. After 15 min of venous air embolism, PAP and PVR increased significantly in both groups. Between-group comparison showed that during VAE the PVR of Pluronic-treated animals was significantly higher as compared to the PVR of control animals. In both groups, VAE led to arterial hypoxia and hypercapnia, as well as a significant increase in physiologic shunt fraction and a significant reduction of $\dot{V}_A$ and MAP. The pulmonary CO_2 elimination was significantly reduced by 18 ± 13% in the control group, whereas the effect was not significant in the Pluronic-treated group. Furthermore, in the control group, $\dot{V}_A/\dot{Q}$ was significantly reduced whereas the effect was not significant in the Pluronic-treated group.

Second treatment (during continuous VAE)

The results after a second treatment with Pluronic F-68 while the animals were still receiving continuous VAE are listed in Table 2. Before the second treatment with Pluronic F-68 or physiologic saline there were no statistical differences between the baseline values in the two groups.

Between-group comparison of data obtained 15 min after the second Pluronic treatment showed that the PAP and the PVR of treated animals were higher as compared to the control animals, whereas the $\dot{Q}_{sp}/\dot{Q}_t$ of the Pluronic-treated group was significantly lower as compared to that of the control group.

No arterial bubbles were detected in the left atrium or aorta of any pigs from either of the two groups.

DISCUSSION

The present study showed that animals pretreated with Pluronic F-68 had a higher PVR as compared to nontreated animals. After the second treatment during continu-

Table 1: Physiologic Parameters (mean ± SD Before Continuous Air Infusion (baseline) and After 15 min of Continuous Air Infusion (embolized) in Control Swine and in Swine Pretreated With 1 ml • kg^{-1} of a 5% Pluronic F-68 Solution

	Control Group		Pluronic-treated Group		Between-group Comparison	
Parameter	Baseline	Embolized	Baseline	Embolized	Baseline	Embolized
PAP, mmHg	13.0 ± 3.0	31.1 ± 4.4[a]	13.0 ± 1.6	33.3 ± 3.0[a]	NS	NS
MAP, mmHg	91.9 ± 8.6	80.8 ± 9.1[b]	96.1 ± 15.6	82.9 ± 20.1[b]	NS	NS
CVP, mmHg	1.4 ± 1.0	2.7 ± 1.4[b]	3.8 ± 3.0	5.0 ± 2.9	NS	NS
Q, ml • kg^{-1} • min^{-1}	265 ± 33	270 ± 55	241 ± 34	216 ± 43	NS	NS
PVR, mmHg • ml^{-1} • min^{-1} • kg^{-1}	0.05 ± 0.01	0.12 ± 0.03[c]	0.06 ± 0.01	0.16 ± 0.02[a]	NS	[d]
SVR, mmHg • ml^{-1} • min kg	0.35 ± 0.08	0.30 ± 0.07	0.39 ± 0.07	0.37 ± 0.13	NS	NS
Pa_{O_2}, kPa	17.1 ± 1.3	8.3 ± 0.9[a]	17.2 ± 1.1	9.6 ± 1.5[a]	NS	NS
Pa_{CO_2}, kPa	4.2 ± 0.4	5.7 ± 0.4[a]	4.1 ± 0.4	5.5 ± 0.6[c]	NS	NS
Q_{sp}/Qt	0.04 ± 0.01	0.31 ± 0.07[a]	0.03 ± 0.01	0.21 ± 0.08[c]	NS	NS
VO_2, ml • kg^{-1} • min^{-1}	11.2 ± 1.1	10.6 ± 1.7	10.3 ± 0.3	9.7 ± 1.1	NS	NS
VCO_2, ml • kg^{-1} • min^{-1}	8.2 ± 0.9	6.7 ± 1.1[c]	7.7 ± 0.9	6.6 ± 1.0	NS	NS
V_A, ml • kg^{-1} • min^{-1}	197 ± 19	112 ± 14[a]	188 ± 30	113 ± 26[b]	NS	NS
V_A/Q	0.75 ± 0.14	0.42 ± 0.08[b]	0.79 ± 0.18	0.53 ± 0.11	NS	NS

Within-group comparison: [a]$P < 0.001$, [b]$P < 0.05$, [c]$P < 0.01$; between-group comparison, [d]$P < 0.05$.

Table 2: Physiologic Parameters (mean ± SD) During Continuous i.v. Air Infusion (0.05 ml • kg^{-1} • min^{-1}) Before and 15 min After a Second i.v. Injection With Saline (control group) or 1 ml • kg^{-1} of 5% Pluronic F-68

	Control Group		Pluronic-treated Group		Between-group Comparison	
Parameter	Before 2d treatment	Treated	Before 2d treatment	Treated	Baseline	Treated
PAP, mmHg	28.1 ± 1.5	27.4 ± 1.7	29.4 ± 2.4	30.9 ± 1.3	NS	[a]
MAP, mmHg	83.3 ± 12.5	84.0 ± 15.1	83.7 ± 18.6	91.5 ± 22.2	NS	NS
CVP, mmHg	2.2 ± 1.4	2.1 ± 1.2	4.2 ± 2.3	4.7 ± 2.8	NS	NS
Q, ml • kg^{-1} • min^{-1}	347 ± 53	333 ± 37	294 ± 50	264 ± 60	NS	NS
PVR, mmHg ml^{-1} • min^{-1} • kg^{-1}	0.08 ± 0.01	0.08 ± 0.01	0.10 ± 0.03	0.12 ± 0.03	NS	[b]
SVR, mmHg • ml^{-1} • min^{-1} • kg^{-1}	0.24 ± 0.05	0.25 ± 0.06	0.27 ± 0.05	0.34 ± 0.11	NS	NS
Pa_{O_2}, mmHg	8.4 ± 1.1	8.5 ± 1.0	9.9 ± 1.2	9.7 ± 1.1	NS	NS
Pa_{CO_2}, mmHg	6.8 ± 0.7	6.9 ± 0.6	6.3 ± 0.9	6.4 ± 0.9	NS	NS
Q_{sp}/Q_t	0.31 ± 0.09	0.32 ± 0.07	0.23 ± 0.06	0.23 ± 0.04	NS	[b]
V_{O_2}, ml • kg^{-1} • min^{-1}	11.8 ± 1.6	11.0 ± 2.0	10.3 ± 1.2	10.0 ± 2.0	NS	NS
V_{CO_2}, ml • kg^{-1} • min^{-1}	7.0 ± 1.6	7.0 ± 1.7	7.4 ± 0.6	6.9 ± 0.7	NS	NS
V_A, ml • kg^{-1} • min^{-1}	98 ± 29	99 ± 29	113 ± 19	103 ± 25	NS	NS
V_A/Q	0.30 ± 0.11	0.30 ± 0.11	0.39 ± 0.06	0.40 ± 0.11	NS	NS

Between-group comparison, [a] $P < 0.01$, [b] $P < 0.05$.

ous air infusion, treated animals in addition had a higher pulmonary artery pressure and a lower physiologic shunt fraction as compared to the control group.

After both the first and the second treatment, the Pluronic-treated group had values of PVR that were significantly higher than those of the control group. It therefore seems that Pluronic treatment, in combination with VAE, increases the response in the vascular resistance of the pulmonary circulation.

Because bubble size in plasma decreases with the addition of surface-active substances (13) it is likely that in Pluronic-treated pigs a large number of smaller bubbles is produced from a given amount of intravenously introduced gas. These smaller bubbles are probably also transported further into the pulmonary circulation before they are trapped in the vessels. It has been suggested that the hemodynamic response to embolization of arterioles and capillaries by emboli smaller than 100 μm in diameter is in part due to vasoconstriction superimposed on mechanical obstruction (14). To clarify this, the obstruction of pulmonary arteries (caused by embolism) only results in a mechanical blocking of the perfusion, whereas obstruction of arterioles results in an additional reduction of perfusion due to vasoconstriction. It is therefore possible that the higher response in PVR in the Pluronic-treated group is because the smaller bubbles penetrated further into the pulmonary system and elicited additional vasoconstriction in arterioles. This suggested mechanism is supported by our previous report of significant changes in PAP after i.v. introduction of small volumes (0.5 ml) of microbubbles with a diameter ≤50 μm (15).

The vasoconstrictory response, proposed to be responsible for the difference in magnitude of PVR response, could also answer for the between-group difference in PAP noted after the second surfactant treatment (Table 2). The between-group difference in $\dot{Q}_{sp}/\dot{Q}_t$ after the second treatment with Pluronic F-68 could also be linked to a difference in bubble size in the two groups. Occlusion of arteries (by large bubbles) will obstruct blood flow to a larger part (surface area) of the pulmonary arterial tree than will obstruction of smaller arterioles (16). This is because when arterioles are blocked, the flow can be redirected through other unblocked arterioles.

Lack of between-group differences in any physiologic variable after 60 min of air infusion (i.e., baseline values presented in Table 2) could indicate that the effects of Pluronic are only short-term. One may also speculate if this is why the responses observed 40 min after the first Pluronic treatment seemed to be less than the responses observed 15 min after the second infusion.

How agents that lower surface tension affect air embolism has previously been studied by several authors (5, 17–19), and it has been demonstrated that treatment with antifoam agents has reduced mortality resulting from coronary bubbles in dogs and mortality in rats after rapid decompression (17, 18). Fluorocarbon solutions, which are known for their extremely low surface tension values (20), have also been used beneficially for the treatment of cerebral air embolism in rats (19). However, the results of Pluronic treatment reported in the present study do not seem to explain the decreased mortality demonstrated in the above-mentioned studies. Perry and colleagues (5) reported a decrease in cardiorespiratory response to VAE when dogs were treated with Pluronic F-68: Pluronic treatment protected against a drop in MAP and $\dot{Q}$, and reduced the drop in Pa_{O_2}. Our study showed that VAE resulted in a drop in MAP and that $\dot{Q}$ was not affected in any of the two experimental groups. It is possible that these differing effects of VAE are related to differences in the physiology

of the two species (dog and pig) used in the two studies, or to the fact that Perry and co-workers (5) exposed their animals to multiple air infusions without differing between these when treating the data.

Butler and Hills (6) argue that an increase of surface-active components in the blood may have the fatal effect of lowering the threshold (or volume required) for transpulmonary passage of venous gas bubbles into the arterial circulation. The effect of arterial bubbles is serious, especially if they enter the cerebral circulation (21, 22). In the present study, no arterial bubbles were detected in either of the two groups. The reason for this is probably that the amount of gas that entered the pulmonary circulation was effectively excreted to the alveoli. It is therefore possible that differences in transpulmonary passage of venous bubbles might have been detected at a higher infusion rate. On the other hand, one should expect the excretion of gas in the bubbles to be further enhanced as the bubbles are forced into the pulmonary capillaries in the Pluronic-treated group, where the diffusing distance to the alveolar space is very short.

In conclusion, except for the greater increase in PVR caused by air infusion in surfactant-treated animals, that was also evident after a second treatment during the air infusion, treatment with the surface-lowering agent Pluronic F-68 before or during i.v. air infusion did not significantly modify hemodynamic or ventilatory responses in pigs. We speculate that the minor changes we observed were caused by deeper penetration of the bubbles into the pulmonary arterial tree after surfactant treatment.

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