Venous gas embolism: time course of residual pulmonary intravascular bubbles

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Butler BD, Luehr S, Katz J. Venous gas embolism: time course of residual pulmonary intravascular bubbles. Undersea Biomed Res 1989; 16(1):21–29.—The time course of pulmonary intravascular air emboli was studied in anesthetized dogs. In one series of experiments air was infused into the right atrium at 0.10 ml · kg^{-1} · min^{-1} or 0.25 ml · kg^{-1} · min^{-1} for 15 min or given as a bolus injection of 2 ml/kg at 2 ml/sec. In a second series of experiments venous air was infused into dogs (0.25 ml · kg^{-1} · min^{-1}, 15 min) ventilated with 100% oxygen for 0, 30, or 210 min before the embolization. After the air infusions the animals were allowed to recover, breathing 70% nitrogen:30% oxygen. At 10-min intervals during recovery, the nitrogen was replaced with nitrous oxide (N_2O) for 5 min to expand any residual pulmonary vascular bubbles. Subsequent changes in pulmonary artery pressure (Ppa) and end-tidal carbon dioxide ($P_{ET_{CO_2}}$) concentrations, pulmonary vascular resistance (PVR) and carbon dioxide tensions (Pa_{CO_2}) as a result of the N_2O challenges indicated the presence of residual gas bubbles in the pulmonary arterial system. Residual times of the pulmonary bubbles were 24.5 ± 12.3 min (0.10 ml · kg^{-1} · min^{-1} air dose), 43 ± 10.8 min (0.25 ml · kg^{-1} · min^{-1} air dose), and 17.8 ± 2.5 min (bolus). The latter two were significantly different from each other. With 100% oxygen breathing the residual times were 19 ± 2.2 (0 min), 22 ± 6.7 min (30 min), and 17 ± 4.0 (210 min). These values were reduced significantly when compared to the dogs ventilated with 30% oxygen. The results indicate that after venous air embolism, gas bubbles may remain in the lungs beyond the period when Ppa, PVR, $P_{ET_{CO_2}}$, and Pa_{CO_2} have returned to baseline. One hundred percent oxygen breathing shortens the time that residual bubbles are detected.

air embolism
decompression sickness
nitrous oxide
oxygen ventilation
venous gas embolism

Venous gas embolism has been reported following decompression in deep-sea divers, aviators, and astronauts, during neurosurgery, or during certain diagnostic or therapeutic procedures. With decompression sickness, knowledge of the presence of residual pulmonary intravascular gas is important when considering the safety of repetitive pressure exposures. Second and subsequent decompressions may result in accumulation of excessive volumes of gas in the lungs if inadequate time has elapsed for complete resolution to occur. With clinical cases of venous gas embolism, there

is concern regarding the amount of residual gas remaining in the pulmonary vasculature once surgery resumes.

With decompression the degree of pressure change and extent of denitrogenation will influence the number of venous gas emboli that eventually circulate into the lungs. The length of time that these gas emboli remain as discrete bubbles in the pulmonary vasculature is dependent on the volume of gas introduced and solubility-diffusivity characteristics of the gas. Preoxygenation is one way of limiting the volume of gas bubble formation in the blood by reducing the amount of dissolved tissue nitrogen. Subjects who breathe 100% oxygen before decompression (e.g., astronauts before extravehicular activity) have reduced venous bubbling detected by Doppler ultrasound and a decrease in overall incidence of decompression sickness (1). If a sufficient quantity of gas accumulates in the pulmonary microcirculation, edema formation can result (2). The added risk of cerebral embolism exists if the bubbles cross the pulmonary microcirculation (3–6).

With clinical venous gas embolism, Munson et al. (7) and others (8, 9) have suggested the use of N_2O challenges in the inspired gas mixture to amplify intravascular bubbles while simultaneously monitoring pulmonary artery pressure (Ppa) and end-tidal carbon dioxide ($P_{ET_{CO_2}}$), with the aim of determining when it was safe to proceed with an operation. Because N_2O is 34 times more soluble in blood than the nitrogen contained in air bubbles, pulmonary vascular bubbles increase in volume (7, 10) and elicit measurable responses in Ppa, pulmonary vascular resistance (PVR), $P_{ET_{CO_2}}$, and arterial carbon dioxide tensions (Pa_{CO_2}). Changes in these variables indicate the need for further bubble resolution time. This prompted us to undertake the present study with the aim of determining the time course of residual pulmonary intravascular bubbles after embolization with known amounts of venous air, using a N_2O challenge technique. We also examined the length of time that the venous gas emboli remained as discrete bubbles in the lungs with 100% oxygen ventilation.

MATERIALS AND METHODS

Surgery

Dogs were anesthetized with thiopental sodium (25 mg/kg), intubated, and ventilated (Harvard) with nitrogen and oxygen (70:30) at a tidal volume of 17.5 ml/kg to maintain baseline Pa_{CO_2} at 35–40 mmHg. Anesthesia was maintained with halothane. Pressure-monitoring catheters were placed in the abdominal aorta via the femoral artery for mean arterial pressure (MAP), the pulmonary artery via the right jugular vein for Ppa and thermodilution cardiac output (CO) determination, and the left ventricle via the right carotid artery for left ventricular end-diastolic pressure (LVEDP). Pressures were measured with transducers (Statham P23ID), zero referenced at the right atrial level, and calibrated with a mercury column. The transducers were connected to a multichannel chart recorder. Blood samples were collected from the arterial line for blood gas analysis. $P_{ET_{CO_2}}$ was measured using an infrared analyzer (Datex). PVR was calculated by (Ppa-LVEDP)/CO. The dogs were stabilized for 30–45 min before collection of baseline data.

Venous gas embolism

In the first series of experiments venous gas was infused into the right atrium via the proximal lumen of the pulmonary artery catheter. The air doses were controlled with a reciprocating servo pump (Harvard). Eighteen dogs were divided into 3 experimental groups of 5 each and 1 control group of 3. The control animals (group 1) were ventilated with 70% N_2O:30% oxygen for 60 min without receiving venous air infusions. Group 2 had air infused at 0.10 ml · kg^{-1} · min^{-1} for 15 min (total vol = 33 ± 2.7 ml); group 3 at 0.25 ml · kg^{-1} · min^{-1} for 15 min (total vol = 94 ± 1.4 ml); and group 4 received a bolus air injection of 2 ml/kg (total vol = 48 ± 2.8 ml) injected at a rate of 2 ml/sec. In another 3 animals receiving 0.25 ml · kg^{-1} · min^{-1} for 15 min, the first N_2O challenge followed 30 min after the infusion. No animal was embolized more than once.

Hemodynamic data were collected before and immediately after the air infusions and at 10 min postinfusion with the animals breathing nitrogen and oxygen. After 10 min of recovery the nitrogen was switched to 70% N_2O for 5 min to amplify any residual pulmonary vascular bubbles. This sequence of 10 min nitrogen-oxygen breathing followed by 5 min of nitrous oxide-oxygen breathing was repeated 3 times. After each N_2O challenge, the changes in Ppa, PVR, Pa_{CO_2}, and $P_{ET_{CO_2}}$ were recorded, as well as the total elapsed time following the embolizations. Owing to the stability of these parameters during the baseline period, any change from the preceding sample time that was equal to or greater than 2 mmHg for Ppa and $P_{ET_{CO_2}}$, 10% for PVR, and 3 mmHg for Pa_{CO_2} was considered a positive indicator for the presence of residual pulmonary vascular gas (11).

In the second series of experiments 15 dogs were divided into 3 groups of 5 each. The dogs were embolized at 0.25 ml · kg^{-1} · min^{-1} for 15 min while ventilated with 100% oxygen for 0, 30, or 210 min before and during the air infusions. After the air infusions, the presence of residual gas bubbles was determined using the N_2O challenges as previously described. Four control dogs were ventilated with 100% oxygen and received 15 N_2O challenges without the presence of gas bubbles.

Statistics

Comparison of physiologic data measured before and after venous gas infusions or between doses were made using analysis of variance (one-way) with Bonferroni-corrected Student's t test for determination of significance ($P < 0.05$).

RESULTS

The mean changes in Ppa, PVR, Pa_{CO_2}, and $P_{ET_{CO_2}}$ after the venous gas infusions are shown in Tables 1 and 2. There were no changes in Ppa, PVR, Pa_{CO_2}, or $P_{ET_{CO_2}}$ in the control group that had N_2O challenges without gas embolism. Ppa showed a greater response to the bolus gas infusions as compared to the 0.10 ml · kg^{-1} · min^{-1} infusion ($P < 0.05$). PVR differences between the lower infusion dose and both the bolus infusion and the 0.25 ml · kg^{-1} · min^{-1} infusion were also significant (Table 1). With oxygen ventilation, significant differences were observed between the 0 and 210 min preoxygenation times for Ppa and PVR (Table 2).

TABLE 1
PULMONARY DATA FOLLOWING THREE DOSES OF VENOUS GAS EMBOLISM

	Ppa, mmHg			PVR, dynes · sec · cm^{-5}		
Venous gas dose	0.10	0.25	bolus	0.10	0.25	bolus
Baseline	12 ± 3.0	12 ± 2.4	11 ± 1.6	226 ± 102	138 ± 87	196 ± 91
Venous gas embolization	17[a] ± 3.6	26[b] ± 2.6	31[a,b] ± 4.1	409[a,b,c] ± 117	731[a,b] ± 99	785[b,c] ± 205
	Pa_{CO_2}, mmHg			PET_{CO_2}, mmHg		
Venous gas dose	0.10	0.25	bolus	0.10	0.25	bolus
Baseline	39 ± 6.6	35 ± 3.8	38 ± 1.1	33 ± 4.9	29 ± 5.8	34 ± 3.0
Venous gas embolization	46 ± 10.0	48[b] ± 8.4	44[b] ± 3.4	20[b] ± 2.0	12[b] ± 4.1	20 ± 7.5

Data are means ± SD. Venous gas doses, 0.10 and 0.25 ml · kg^{-1} · min^{-1} (15 min); bolus = (2 ml/kg), 2 ml/sec. [a]$P < 0.05$ (0.10 vs. bolus); [b]$P < 0.05$ compared to baseline; [c]$P < 0.05$ (0.10 vs. 0.25).

TABLE 2
PULMONARY DATA FOLLOWING VENOUS GAS EMBOLISM IN OXYGEN VENTILATED DOGS

	Ppa, mmHg			PVR, dynes · sec · cm^{-5}		
Preoxygenation, min	0	30	210	0	30	210
Baseline	11 ± 1.9	14 ± 4.9	16 ± 5.6	225 ± 86	258 ± 134	514 ± 319
Venous gas embolization	28[a,b] ± 5.1	28[a] ± 4.3	37[a,b] ± 9.8	963[a,b] ± 362	1039[a] ± 289	1454[a,b] ± 731
	Pa_{CO_2}, mmHg			$PET\text{-}_{CO_2}$, mmHg		
Preoxygenation, min	0	30	210	0	30	210
Baseline	36 ± 2.2	35 ± 2.6	34 ± 5.4	34 ± 4.4	32 ± 2.5	27 ± 3.1
Venous gas embolization	51[a] ± 6.7	48[a] ± 5.2	54[a] ± 13.4	16[a] ± 5.8	15[a] ± 3.6	16[a] ± 2.5

Venous gas emboli infused at 0.25 ml · kg^{-1} · min^{-1} (15 min). Data are means ± SD. [a]$P < 0.05$ compared to baseline; [b]$P < 0.05$ (0 vs. 210 min preoxygenation).

The results of the N_2O challenges during recovery from the gas infusions are shown in Figs. 1 and 2 as the time (min) that bubbles remained in the pulmonary vasculature. They were 43 ± 10.8 min for the 0.25 ml · kg^{-1} · min^{-1} group, 24.5 ± 12.3 min for the 0.10 ml · kg^{-1} · min^{-1} group, and 17.8 ± 2.5 min for the bolus group. The latter value was significantly shorter than the 0.25 ml · kg^{-1} · min^{-1} group. The dogs that had N_2O challenges beginning 30 min after the embolizations (0.25 ml · kg^{-1} · min^{-1}) demonstrated bubble longevity times of 35.7 ± 2.5 min. This value was not significantly different from the first 0.25 ml · kg^{-1} · min^{-1} group that had N_2O challenges beginning 10 min postembolization.

The oxygen-ventilated dogs had residual pulmonary gas bubbles 19 ± 2.2 min (0 min preoxygenation), 22 ± 6.7 min (30 min preoxygenation), and 17 ± 4.0 min (210 min preoxygenation). These times were not significantly different from each other,

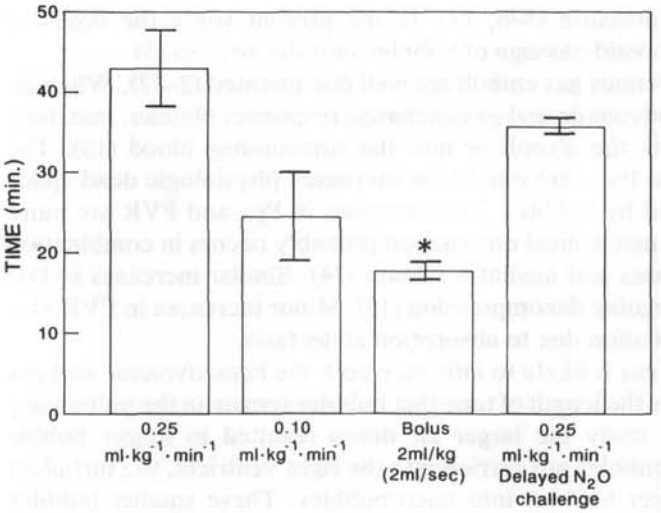

Fig. 1. Mean times (± SEM) for residual pulmonary intravascular bubbles following infusion at 3 doses. Delayed N_2O challenge began 30 min after the gas infusions. * = $P < 0.05$, bolus vs. 0.25 ml · kg^{-1} · min^{-1}.

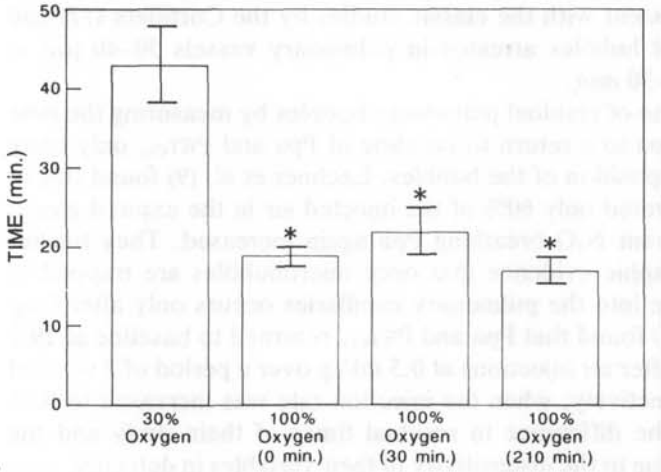

Fig. 2. Mean times (± SEM) for residual pulmonary intravascular bubbles after infusion with 100% preoxygenation for 0, 30, or 210 min vs. 30% oxygen ventilation. Venous gas dose was 0.25 ml · kg^{-1} · min^{-1} for 15 min. * = $P < 0.05$ vs. 30% oxygen ventilation.

although compared to the same gas embolism dose (0.25 ml · kg^{-1} · min^{-1}, 15 min) in dogs ventilated with 30% oxygen (43 ± 10.8 min) the difference was significant ($P < 0.05$).

DISCUSSION

The results of this study suggest that venous gas emboli can remain in the pulmonary vasculature as discrete bubbles for periods lasting up to 43 ± 10.8 min in dogs ventilated with oxygen and nitrogen (30:70%). With 100% oxygen ventilation these values are reduced significantly to 19 ± 2.5 min. Disappearance of the bubbles from the lungs results from the gas diffusing into the surrounding blood, tissues, or alveolar spaces. Additionally, arterialization of venous bubbles through the pulmonary microcirculation is reported after large volumes of infused gas or with rapid decompression

from elevated atmospheric pressure (3–6, 12). In the present study the doses of venous gas were selected to avoid passage of bubbles into the arteries (3).

Physiologic responses to venous gas emboli are well documented (2–12). When air infusions are constant, hemodynamic and gas exchange responses plateau, matching the dissipation of the gas via the alveoli or into the surrounding blood (13). The decrease in $P_{ET_{CO_2}}$ and rise in Pa_{CO_2} are due to the increased physiologic dead space as vessels become obstructed by bubbles. The increases in Ppa and PVR are more complex in their etiology, as mechanical obstruction probably occurs in combination with both neurogenic responses and mediator release (14). Similar increases in Ppa were reported for dogs undergoing decompression (15). Minor increases in PVR also may occur with oxygen ventilation due to absorption atelectasis.

The volume of the venous gas is likely to influence both the hemodynamic and gas exchange responses as well as the length of time that bubbles remain in the pulmonary vasculature. In the present study the larger air doses resulted in longer bubble residence times. As venous bubbles are carried into the right ventricle, the turbulent blood flow fractures the larger bubbles into microbubbles. These smaller bubbles then pass into the pulmonary microcirculation. Josephson and Ovenfors (16) reported that pulmonary responses to venous air injected at 2 ml/kg over 20–30 sec persisted for 14–22 min. This is consistent with the classic studies by the Curtillets (17) and Knisely (18) who found that bubbles arrested in pulmonary vessels 30–40 μm in diameter and dissipated in 5–30 min.

Determining the time course of residual pulmonary bubbles by measuring the time elapsed from the embolization to a return to baseline of Ppa and $P_{ET_{CO_2}}$ only, may not accurately reflect the disposition of the bubbles. Lechner et al. (9) found this to be the case when they recovered only 60% of the injected air in the expired gases, but noted that with subsequent N_2O breathing Ppa again increased. They further concluded from cinematographic evidence that once microbubbles are trapped in small arterioles their passage into the pulmonary capillaries occurs only after long delays. Drummond et al. (11) found that Ppa and $P_{ET_{CO_2}}$ returned to baseline at 19.7 and 15.3 min, respectively, after air injections at 0.5 ml/kg over a period of 2 sec and 23.8 min and 19.4 min, respectively, when the injection rate was increased to 0.75 ml/kg. An explanation for the difference in residual times of their study and the present results are possibly due to the insensitivity of their variables in detecting very small volumes of residual gas. With decompression sickness, Lynch et al. (5) and Powell (19) reported that the number of bubbles was significantly reduced after 10–30 min.

With continued gas infusion or with multiple episodes of gas embolism, as can occur with repetitive decompressions, a greater number of pulmonary arterioles become obstructed and Ppa and PVR increase. This greater number of bubbles increases the total surface area in contact with the alveolar vessel walls, thereby increasing the diffusional exchange (20). Gas exchange has also been shown to occur at the pulmonary arteriolar level (21). Verstappen et al. (13) concluded that larger volumes of gas not only increased the area for diffusional exchange but also raised Ppa and therefore the pressure inside of the bubbles, so that net movement of gas into the alveoli was accentuated. Bubble size may also affect the Ppa and PVR response to the N_2O challenges. With decompression sickness the diameters of the bubbles range from 4 μm (22) to 700 μm (23), with a majority in the 19–150 μm range, whereas those in the present study were initially 500 μm, although fracture into

smaller sizes was likely. Catron et al. (15) suggested that with decompression sickness many more microvessels in the lungs become obstructed than with venous air infusions. This being the case, growth of bubbles with N_2O challenges would have little effect on PVR where microvessels are already obstructed, but would worsen the response with larger, partially obstructed vessels if complete occlusion resulted.

The length of time that bubbles remain trapped at a particular vascular site is partially determined by the diffusibility of the gas that reacts with the surrounding red cells, plasma, and tissues. Mass transfer rates of the gases depend on solubility and diffusion coefficients and partial pressure gradients. Breathing gases of increased solubility or diffusivity as compared to nitrogen will increase bubble volume via counterdiffusive phenomena. Although the diffusivity (D) of N_2O is approximately equal to that of N_2 ($DN_2O = 2.10 \times 10^{-5}$ cm^2/sec vs. $DN_2 = 1.99 \times 10^{-5}$ cm^2/sec in water at 25°C) the solubilities are quite different (N_2O = 0.455 ml N_2O/ml blood vs. N_2 = 0.0158 ml N_2/ml blood in blood at 37°C) (24). This 30-fold increase in the solubility:diffusivity ratio causes nitrogen bubbles in the blood to grow in size as the N_2O levels in the surrounding blood increase (15). Ventilating embolized dogs with oxygen and N_2O therefore favors the growth of air bubbles; however, upon return to nitrogen and oxygen breathing, the N_2O leaves rapidly (7). The greatest change in volume of the bubbles occurs when the gas mixture is switched, either adding or subtracting the N_2O (10). Bubble longevity may also be affected by boundary conditions where the outward diffusion of gases is assisted by the convective movement of flowing blood (25). Additionally, any recruitment of surface-active molecules within the blood to the air:blood interface may alter the surface tension of the bubbles, thereby affecting the rate of resorption (26). N_2O challenges in the present study were used to demonstrate the presence of residual intravascular gas bubbles. It is because of its ability to expand bubbles that N_2O use is not advised in clinical cases that are at high risk of venous embolism (27). The detrimental effects of N_2O-oxygen ventilation in rats following decompression were reported by Van Liew (28).

When the residual times for the bubbles from the 0.25 ml · kg^{-1} · min^{-1} group with N_2O challenges occurring 10 min postinfusion were compared to the animals receiving the same venous air dose but with the first N_2O challenge occurring 30 min postinfusion, the difference was not significant. This indicates that the multiple N_2O challenges did not alter bubble longevity. Using physiologic indicators in combination with N_2O challenges to detect residual gas bubbles has been suggested for certain procedures that are at high risk for venous embolization (e.g., seated neurosurgery) (6, 7). Others have reported that the early detection of small volumes of venous air is facilitated with N_2O utilization, although circulatory failure is possible when larger volumes are entrained (29). When there is no intravascular gas present, N_2O has little effect on pulmonary hemodynamic parameters (30). Further, our results demonstrate that larger volumes of infused gas remain longer in the pulmonary circulation and that similar volumes delivered at different rates do not alter residual times. In the oxygen ventilation experiments it was evident that the longevity of pulmonary vascular bubbles was reduced significantly regardless of the length of preoxygenation time (Fig. 2). This is not to say that prolonged preoxygenation would not affect the degree of bubble formation with decompression sickness; the opposite of this has been shown to exist (1). However, if venous bubbles are produced with decompression sickness then the advantageous effects of oxygen ventilation are further demonstrated in this study. Therapeutic oxygen ventilation after embolization, especially

with compression therapy for decompression sickness, is widely accepted (31). This standard of practice is based on the enhanced absorption of the nitrogen in the bubble into the surrounding oxygenated blood. The remaining oxygen is metabolized. The gas infused in this study does not necessarily correspond exactly to decompression sickness, although the obstruction of pulmonary vessels and associated symptoms are similar. The results of this study describe the residual time course of pulmonary intravascular gas after venous infusion and the influence of 100% oxygen ventilation.

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