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Nitrous Oxide Intensifies the Pulmonary Arterial Pressure Response to Venous Injection of Carbon Dioxide in the Dog

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To determine the effect of nitrous oxide on the body's response to venous carbon dioxide (CO_2) embolization, the authors compared changes in mean pulmonary arterial pressure (MPAP) following intravenous injections of CO_2 in pentobarbital-anesthetized dogs breathing 100 per cent oxygen (O_2) or nitrous oxide–oxygen, 79:21 per cent (N_2O). When CO_2 was infused intravenously in seven dogs at a rate of 3 ml/kg/min the volume of injected CO_2 needed to increase MPAP to 40 per cent above control during breathing of O_2 was approximately 5.5 times the volume necessary during inhalation of N_2O. In a second group of eight dogs, breathing N_2O, compared with O_2 or air, resulted in a significantly greater increase and duration of increase in MPAP following a bolus injection of CO_2 of 20, 40 or 80 ml. The data suggest that breathing nitrous oxide intensifies and prolongs the effect of CO_2 bubbles in blood. While the magnitude of insult following intravenous injection of CO_2 is about 6.5 times less than that for a similar volume of air, avoidance of nitrous oxide should be considered in management of patients in whom CO_2 embolism is possible. (Key words: Anesthetic gases: nitrous oxide. Carbon dioxide: absorption. Embolism: air; carbon dioxide.)

ARTERIAL OR VENOUS gas embolism is possible with a variety of diagnostic and surgical procedures, and may cause serious circulatory impairment. The magnitude of risk depends on a variety of factors, including the type and volume of gas embolized[1,2] and the nature of the inspired gas.[3,4] Carbon dioxide (CO_2) insufflation has been advocated for some procedures (*e.g.*, laparoscopy, open-heart surgery) to lessen the consequences of embolization.[5–7] Carbon dioxide is chosen because its high blood solubility insures rapid absorption by the blood and in turn it is readily eliminated via the lungs.

Movement of a gas from a space into the tissue–blood environment or vice versa is related to gas solubility and partial pressure difference. Recently, we found in dogs that isolated segments of small intestine that contain CO_2 decrease in volume less rapidly during inspiration of nitrous oxide as compared with 100 per cent oxygen. We believe this phenomenon occurs because nitrous oxide, a gas only slightly less soluble than CO_2,§ rapidly transfers into the gas space containing CO_2. The ingress of nitrous oxide compensates for some of the loss of CO_2 and also dilutes the CO_2, thereby decreasing its partial pressure and its uptake. If this same sequence occurred following the injection or aspiration of CO_2 into the circulation, breathing nitrous oxide could render lethal an otherwise transient, innocuous CO_2 embolus. To determine the effect of inspired nitrous oxide on the response to a venous CO_2 embolus, we compared changes in mean pulmonary arterial pressure (MPAP) after intravenous administration of CO_2 in anesthetized dogs breathing 100 per cent oxygen and breathing a nitrous oxide–oxygen mixture. We chose to monitor MPAP because it is a sensitive method for detecting venous gas embolization and provides an indication of the magnitude of embolization.[2,10]

Methods and Materials

Male and female dogs of mixed ages and breeds, weighing 17–25 kg, were anesthetized with pentobarbital, 30 mg/kg, iv. Subsequent doses of anesthetic sufficient to maintain immobility were used. Following tracheal intubation with a cuffed tube, the dogs were placed in left lateral recumbency on a heating blanket. Esophageal temperature was maintained at 37–39 C. Inspired oxygen was measured with a Beckman® D-2 oxygen analyzer, and total gas delivery flow rates exceeded 2 l/min. Mechanical ventillation was adjusted to maintain normal pre-embolization end-tidal or arterial blood CO_2 tension as determined by intermittent infrared or electrode analysis. Arterial blood was obtained anaerobically from a catheter placed in the distal aorta via a right femoral-artery cut-down. Arterial oxygen tension (Pa_{O_2}) was measured by electrode in four dogs immediately prior to venous gas embolization. In all cases the Pa_{O_2} was greater than 90 torr. Femoral arterial pressure was measured directly with a strain gauge and pulmonary arterial pressure was similarly obtained from a balloon-tipped catheter advanced from the right femoral vein. Successful placement of the catheter was confirmed by

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§ Ostwald solubility coefficients in human whole blood at 37 C are 0.49 for CO_2[8] and 0.47 for N_2O[9].

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visualizing appropriate pressure-wave patterns on a recorder. The recorded pressures were taken during the end-expiratory phase of the breathing cycle and meaned electronically. A third catheter was placed percutaneously into the right cephalic vein and used for gas and anesthetic injections.

In seven dogs (Group I), we determined the dose of CO_2 necessary to increase MPAP 40 per cent during breathing of 100 per cent oxygen or nitrous oxide–oxygen, 79:21 per cent. Following control measurements, CO_2 was infused intravenously at a rate of 3 ml/kg/min. Studies were performed in each dog with each inspired gas, and the order in which gases were breathed was varied (five dogs received oxygen first: two dogs received the mixture first). Ten minutes were allowed after measured values had returned to control levels before subsequent CO_2 injections. A 30-min equilibration period beginning at the time the desired inspired oxygen concentration was attained was allowed when changing from one inspired gas to another.

In eight dogs (Group II), we determined the peak increase in MPAP following an intravenous bolus injection of CO_2, 20, 40, or 80 ml, while the dogs breathed 100 per cent oxygen, nitrous oxide–oxygen, 79:21 per cent, or air. Bolus injections were made over 10–20 sec with leak-free glass syringes. We had previously determined that these doses consistently increased MPAP. The order of the gas mixtures breathed was randomized (Latin square); half of the dogs received increasing doses of CO_2, and half, decreasing doses. Breathing air and breathing nitrous oxide–oxygen were always separated by sufficient periods of breathing 100 per cent oxygen to ensure adequate nitrous oxide or nitrogen washout. For comparison, we similarly monitored MPAP changes in six of the Group II dogs following a bolus injection of air, 20 ml.

The results of each intravenous gas dosage in all dogs for each gas breathed were pooled, and are expressed as the mean ± one standard error ($\bar{X} \pm SE$). All data were analyzed on a paired basis using the Student t test. We accepted $P < 0.05$ as significant. The data from the CO_2 bolus injection study were used to plot dose–response linear-regression functions.

Results

No death occurred as a result of the intravenous gas injections. The MPAP recorded just prior to intravenous gas injections in Group II dogs breathing air was 18.0 ± 0.6 torr (n = 30). Breathing the nitrous oxide–oxygen mixture did not change MPAP (18.0 ± 0.5 torr) but breathing 100 per cent oxygen caused a significant decrease in MPAP (15.9 ± 0.3 torr).

TABLE 1. Group I, Intravenous CO_2 Infusions (3 ml/kg/min) in Seven Dogs Breathing Oxygen or Nitrous Oxide

Inspired Gas	Infusion Volume (ml)	Time (Min)	Peak Increase in Mean Pulmonary Arterial Pressure (MPAP) as Per Cent of Control	Time for MPAP to Return to Control (Min)
Oxygen	283 ± 39	4 ± 1	39 ± 2	11 ± 1
Nitrous oxide–oxygen, 79:21 per cent	48 ± 7*	1 ± 1*	45 ± 2	7 ± 1*

* Significantly different from 100 per cent O_2 ($P < 0.05$).

Comparable differences in control MPAP recordings were similarly found in Group I dogs breathing oxygen versus nitrous oxide. There was no significant difference in MPAP prior to intravenous bolus injections of CO_2 or air for a given inspired gas.

In dogs of Group I, the volume of CO_2 necessary to increase MPAP 40 per cent from control was 5.5 times greater during breathing of oxygen than during breathing of nitrous oxide (table 1). Repeat CO_2 injections during breathing of a particular inspired gas in a given animal gave quantitatively similar results.

Although intravenous bolus injections of CO_2 always caused MPAP to increase in dogs of Group II, there was no appreciable difference between results during breathing of oxygen and breathing of air (fig. 1). Breathing nitrous oxide increased MPAP significantly from the oxygen or air values, and these increases generally lasted longer (table 2). An intravenous bolus of air injected into Group II dogs increased MPAP more than the same volume of CO_2, regardless of the gas inspired (table 3). As expected, the greatest increase in MPAP and most prolonged recovery were seen following an air bolus in dogs breathing nitrous oxide.

The average Pa_{O_2} values in three dogs in Group II immediately before intravenous injection of CO_2, 80 ml, were greater than 95 torr for all inspired gases, and pre-embolism Pa_{CO_2} values averaged 38 torr. The Pa_{O_2} usually decreased from control immediately following gas embolism, and the Pa_{CO_2} increased. The lowest average Pa_{O_2} value was 78 torr, and occurred 1 min after embolism while the dogs breathed air. The Pa_{CO_2} values averaged 46 and 41 torr 1 and 2 min after embolism, respectively. End-tidal CO_2 usually increased for one or two breaths following CO_2 embolization, followed immediately by a gradual decline to less than control levels. The magnitude and duration of this decrease depended upon the dose of embolized CO_2 and the nature of the inspired gas. The greatest decrease usually followed the larger injected volumes

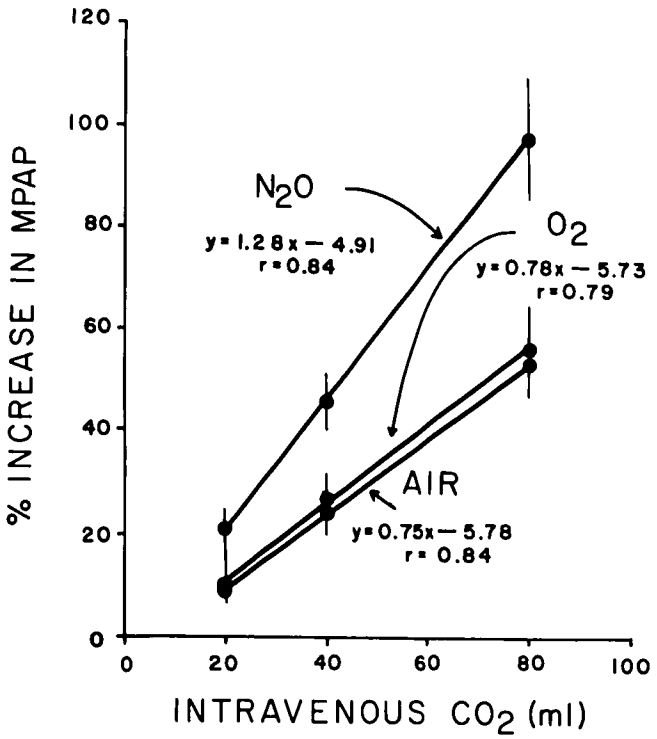

FIG. 1. Percentage increases (mean ± SE) in mean pulmonary arterial pressure (MPAP) following intravenous bolus injections of CO_2 during breathing of air, oxygen (O_2) and nitrous oxide–oxygen (N_2O). The number of dogs studied at each point was eight. The slope of the regression line fitted to the N_2O values for the group breathing was significantly greater than the slope of the regression lines fitted to the O_2- and air-breathing groups.

(regardless the gas type) during breathing of nitrous oxide. End-tidal CO_2 did not increase, but did decrease following intravenous air injections. The end-tidal CO_2 slowly returned to control levels.

Changes in MAP were variable, and appeared to depend upon the intravenous gas dose and the respired gas. Generally, an immediate decrease in MAP was seen following gas injections. When CO_2, 20 or 40 ml, or air, 20 ml, was injected there was often no change, particularly during breathing of air or oxygen. An immediate marked decrease in MAP usually accompanied 80-ml injections in dogs breathing air or oxygen, and all injection dosages in dogs breathing nitrous oxide. The maximum decrease in MAP from control with increasing intravenous doses of CO_2 fit arithmetic coordinates. The equations associated with the inspired gases were: air, $Y = 2.38 - 0.13X$ ($r = -0.54$); oxygen, $Y = 3.44 - 0.17X$ ($r = -0.49$); nitrous oxide, $Y = 5.50 - 0.32X$ ($r = -0.69$), where Y was the maximal decrease in MAP (torr) from control and X was the intravenous dose of CO_2 (ml).

Discussion

Mean pulmonary arterial pressure is a sensitive indicator of venous air embolism, and an increase in pressure quantitatively reflects the size of the embolus. The duration of a positive response also may define the time necessary to resolve the physiologic insult. A slightly less sensitive indicator is a decrease in end-tidal CO_2. The validity of this indicator may decrease if the embolus is CO_2. Mean systemic arterial pressure consistently decreases following large intravenous doses, but does not reveal the presence of small emboli.[2] Our studies with both air and CO_2 as the embolized gases confirm these prior observations.

The increase in MPAP seen following venous gas administration is generally regarded as a direct reflection of increasing pulmonary vascular resistance secondary to a mechanical blockade of the pulmonary circulation by gas bubbles. Mean pulmonary arterial pressure may also be influenced by a variety of physiologic vasoactive substances. For example, hypoxemia, or high levels of CO_2 or nitrous oxide, may produce pulmonary hypertension by acting directly on the blood vessels or by altering autonomic activity.

The increases in MPAP associated with CO_2 injections during breathing of nitrous oxide probably were not related to decreases in oxygenation, because the Pa_{O_2} values during breathing of air and oxygen–nitrous oxide and following embolization were similar. In addition, any direct effect of nitrous oxide on the pulmonary vessels should be common to both control and experimental periods.[11,12] However, we cannot rule

TABLE 2. Group II, Average (±SE) Times to Return to Control Mean Pulmonary Arterial Pressure Following Intravenous Bolus Injections of CO_2 in Eight Dogs

Intravenous Dose (ml)	Recovery Time (Min)		
	Oxygen	Air	Nitrous Oxide–Oxygen, 79:21 Per Cent
20	1.3 ± 0.3*	2.4 ± 0.4*	4.7 ± 0.5*
40	3.1 ± 0.5	3.9 ± 0.5	5.9 ± 0.7*
80	4.8 ± 0.5	4.8 ± 0.9	7.0 ± 1.0

All values within an inspired gas grouping were significantly different ($P < 0.05$).

* All comparisons of results within an intravenous dose grouping differed by at least $P < 0.05$.

TABLE 3. Group II, Average (±SE) Percentage Increases in Mean Pulmonary Arterial Pressure After a 20-ml Intravenous Bolus Injection of CO_2 or Air in Six Dogs

Injected Gas	Increase in Mean Pulmonary Arterial Pressure (Per Cent)		
	Oxygen	Air	Nitrous Oxide–Oxygen, 79:21 Per Cent
CO_2	10 ± 3	10 ± 3	23 ± 5*
Air	68 ± 13	87 ± 17	148 ± 18*

All values within an inspired gas grouping were significantly different ($P < 0.005$).

* All nitrous oxide–oxygen comparisons within an injected gas grouping showed significant differences ($P < 0.05$).

out the possibility of local hypoxia that was greater during breathing of nitrous oxide. This might add to the increase in pulmonary arterial resistance and pressure and thus exaggerate the difference between the effects of breathing nitrous oxide and breathing oxygen.

That the increase in MPAP associated with intravenous CO_2 administrations was not merely the result of an increase in non-embolic venous CO_2 content is supported by the accompanying increases in Pa_{CO_2} and decreases in end-tidal CO_2 and MAP. These results suggest an increase in physiologic respiratory dead space and a decrease in cardiac output, as might occur with mechanical blockage of portions of the pulmonary circulation, and are similar to observations following air embolism in this and other studies.[10,13,14]

Our results confirm those from earlier investigations in dogs, which showed greater tolerance to intravenous injections of CO_2 than to injections of air.[1,15–17] These data support the recommendation that CO_2 be used rather than air for diagnostic or therapeutic maneuvers involving a risk of venous or arterial gas embolization. Our results go beyond those obtained previously in that we have demonstrated that breathing nitrous oxygen enhances the risk associated with CO_2 embolization. We found that lesser quantities of intravenously infused CO_2 are necessary to increase MPAP, and that the magnitude and duration of the increase in MPAP are greater in dogs when they breathe nitrous oxide, compared with oxygen. We believe that these data support the hypothesis that nitrous oxide intensifies and prolongs the presence of CO_2 bubbles in blood. This occurs because N_2O rapidly enters the gas space containing CO_2, adding to the gas volume and diluting the CO_2. The CO_2 dilution decreases its partial pressure difference relative to blood, which thereby slows the efflux of CO_2 from the bubble space.

Although nitrous oxide magnified the circulatory effect of CO_2 emboli, the effect was only about a third that seen following air injections during breathing of oxygen. The quantitative difference in circulatory responsivenesses to air embolization and CO_2 embolization during breathing of nitrous oxide depends primarily upon the difference in solubilities between nitrogen and CO_2 and the differential exchange of these gases into and out of gas spaces in the presence of nitrous oxide. Nitrogen is relatively insoluble in blood, while CO_2 has approximately the same solubility as nitrous oxide. Consequently, the rapid entrance of nitrous oxide from the blood expands an air (nitrogen) embolus,[3,13,18,19] while only retarding the rate of decrease of a CO_2 bubble.

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