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Detection and Hemodynamic Consequences of Venous Air Embolism

Does Nitrous Oxide Make a Difference?

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Volume expansion of intravascular air by nitrous oxide (N_2O) may improve the sensitivity of monitors used to detect venous air embolism (VAE) and/or exacerbate hemodynamic changes following VAE. The purpose of this study was to determine if the administration of N_2O alters the sensitivity (*i.e.*, threshold of detection) of monitors used to detect VAE or the hemodynamic consequences of VAE. Twenty-one dogs were monitored for VAE with precordial Doppler ultrasound, transesophageal echocardiography (TEE), changes in end-tidal carbon dioxide tension (ET_{CO_2}), and changes in pulmonary artery pressure (PAP). Venous air was infused at rates between 0.005 and 0.4 ml · kg^{-1} · min^{-1} during 1 MAC (total anesthetic level) of isoflurane with and without 50% N_2O (group 1, n = 7) or isoflurane with and without 75% N_2O (group 2, n = 7). The mean quantity of infused air necessary to elicit a positive response in both the presence and absence of N_2O was calculated for each monitor. Positive responses were defined as follows: unmistakable audible change in frequency on Doppler ultrasound, visualization of densities consistent with air bubbles in the right cardiac chambers or outflow tract on TEE, a decrease in ET_{CO_2} greater than or equal to 2 mmHg, and an increase in mean PAP greater than or equal to 3 mmHg. In group 3 (n = 7), venous air was infused at rates between 0.1 and 0.8 ml · kg^{-1} · min^{-1} during 1 MAC (total anesthetic level) of isoflurane with and without 50% N_2O. In group 3, N_2O administration was discontinued immediately upon Doppler detection of VAE and air infusion continued until mean arterial pressure (MAP) decreased by 10 mmHg. The volume of VAE necessary to elicit a positive response with the TEE and Doppler was not significantly different in the presence and absence of N_2O. However, VAE was detected by changes in ET_{CO_2} and PAP with smaller volumes of infused air in the presence of both 50% and 75% N_2O in oxygen (O_2) compared to 100% O_2. In group 3, the volume of VAE necessary to decrease the MAP by 10 mmHg was not influenced by N_2O. The authors conclude that administration of N_2O does not improve the sensitivity (*i.e.*, reduce the threshold of detection of air emboli) of the TEE or precordial Doppler but does improve the sensitivity of ET_{CO_2} and PAP monitoring in the detection of VAE. In isoflurane-anesthetized dogs, during continuous intravenous infusion of air at rates up to 0.8 ml · kg^{-1} · min^{-1}, hemodynamic compromise is not worsened in animals receiving 50% N_2O if N_2O administration is discontinued immediately upon Doppler detection of VAE. (Key words: Complications: air embolism. Embolism: air. Anesthetics, gases: N_2O. Measurement: capnometer; Doppler; transesophageal echocardiography.)

AIR-CONTAINING CAVITIES in the body can increase in volume and/or pressure in the presence of nitrous oxide (N_2O) due to the difference in blood–gas solubility between N_2O and nitrogen (N_2).[1] Theoretically, the volume of an air-containing cavity can increase to 200% and 400% of its original volume in the presence of 50% and 75% N_2O, respectively. When venous air embolism (VAE) occurs in the presence of N_2O, the intravascular air bubbles will increase in size as N_2O diffuses into the bubble more rapidly than N_2 can diffuse out.[2] Based upon this volume expansion, it is possible that the sensitivity (*i.e.*,, threshold of detection) of monitors used to detect VAE may be enhanced in the presence of N_2O. In contrast to this potential benefit, Munson and Merrick demonstrated in halothane-anesthetized rabbits that the lethal dose of injected air is decreased by a factor of 3.4 in animals receiving 72–76% N_2O in oxygen (O_2) compared to animals receiving 100% O_2.[3]

Glenski *et al.* have previously determined the relative sensitivity of monitors to detect VAE in dogs whose lungs are mechanically ventilated with 100% O_2.[4] However, there is no study available comparing the sensitivity of monitors to detect VAE in the presence and absence of N_2O. Also, no published study has examined the hemodynamic effects of continuous VAE in the presence and absence of N_2O if N_2O administration is discontinued immediately upon precordial Doppler detection of VAE. The purpose of our study was 2-fold. The purpose of the first part of this study was to determine the effect of N_2O on the sensitivity of four monitors used to detect VAE, namely precordial Doppler ultrasound, transesophageal echocardiography (TEE), changes in end-tidal carbon dioxide tension (ET_{CO_2}), and changes in pulmonary artery pressure (PAP). The purpose of the second part of this study was to determine the volume of VAE necessary to produce hypotension during anesthesia with isoflurane in O_2 compared to anesthesia with isoflurane and 50% N_2O

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in O_2 when N_2O administration was discontinued immediately upon Doppler detection of VAE.

Materials and Methods

With approval of the Animal Care and Use Committee of Mayo Clinic, 21 adult mongrel dogs of either sex were studied. Three groups of 7 dogs each were studied. Group 1 and 2 animals were studied in the first part of the study, and group 3 animals were studied in the second part. In all animals, anesthesia was induced with intravenous thiopental 15–20 mg/kg. The trachea was intubated, and the lungs were mechanically ventilated to maintain Pa_{CO_2} at 35–45 mmHg. Anesthesia was maintained with isoflurane with or without N_2O to achieve 1 MAC total anesthetic level. Expired anesthetic concentrations were monitored with a mass spectrometer. Muscle paralysis was achieved with intravenous vecuronium 0.2 mg/kg initially followed by intravenous infusion at 0.12 $mg \cdot kg^{-1} \cdot h^{-1}$. Lactated Ringer's solution 10 ml/kg intravenous bolus followed by 10 $ml \cdot kg^{-1} \cdot h^{-1}$ was administered to all animals. All dogs remained supine throughout the study.

The right external jugular vein was cannulated percutaneously with an 8-Fr cordis catheter, through which a 7-Fr pulmonary artery catheter was passed into the pulmonary artery. The left external jugular vein was cannulated percutaneously with an 18-G 2-inch intravenous catheter for infusion of air. The femoral artery was cannulated with an 18-G Teflon catheter for measurement of systemic arterial pressure.

Monitoring for VAE consisted of a precordial Doppler ultrasound flow transducer (Medasonics, Mountain View, CA), a 3.5-MHz TEE probe (Diasonics, Inc., Milpitas, CA) interfaced with a 3400 Diasonics phased-array sector echo instrument, a Hewlett-Packard 47210A capnometer to monitor ET_{CO_2}, and a pulmonary artery catheter. The chest was shaved and the precordial Doppler positioned so that a 5-ml agitated saline injection through the left external jugular vein catheter elicited an audible change in Doppler sounds. The TEE probe was positioned to view the right cardiac chambers and ventricular outflow tract. The TEE was not used during part 2 of the study.

PART 1

The purpose of part 1 of the study was to determine if the administration of 50% or 75% N_2O in O_2, compared to 100% O_2, results in detection of smaller volumes of VAE using TEE, precordial Doppler ultrasound, ET_{CO_2}, and/or PAP monitoring.

Real-time TEE and Doppler changes were monitored by a blinded, experienced observer (SB, DAM) during each infusion of air. ET_{CO_2}, right atrial pressure (RAP), PAP, and mean arterial pressure (MAP) were monitored continuously with each air infusion. Using a Harvard infusion pump, air was infused at 0.005, 0.01, 0.05, 0.1, and 0.2 $ml \cdot kg^{-1} \cdot min^{-1}$ in random sequence followed by an infusion at 0.4 $ml \cdot kg^{-1} \cdot min^{-1}$. These rates were selected based upon a previous study of the relative sensitivity of monitors to detect VAE in a canine model.[4] Positive responses were defined (*a priori*) as follows: unmistakable audible change in frequency on Doppler ultrasound; visualization of densities consistent with air bubbles in the right cardiac chambers or outflow tract on TEE; a decrease in ET_{CO_2} greater than or equal to 2 mmHg; and an increase in mean PAP greater than or equal to 3 mmHg. Air infusion was terminated at 6 min or as soon as all four monitors elicited a positive response, whichever occurred first. Subsequent air infusions were not begun until there was no evidence of residual air as detected by TEE or Doppler, and ET_{CO_2}, PAP, MAP, and RAP had returned to baseline levels or remained stable for a minimum of 5 min.

Each dog received air infusions under two different anesthetic conditions. In group 1 (n = 7), venous air was infused during anesthesia with isoflurane in O_2 and during anesthesia with isoflurane and 50% N_2O in O_2. In group 2 (n = 7), venous air was infused during anesthesia with isoflurane in O_2 and during anesthesia with isoflurane and 75% N_2O in O_2. Isoflurane concentration was adjusted in the presence and absence of N_2O to provide a total of 1 MAC anesthetic level. Previously reported values to achieve 1 MAC anesthetic conditions with either isoflurane or N_2O in dogs are 1.5% and 188%, respectively.[5] Based upon these values, the expired concentrations for isoflurane with and without N_2O that were considered to provide 1 MAC total anesthetic level were 1.10% isoflurane with 50% N_2O, 0.90% isoflurane with 75% N_2O, and 1.50% isoflurane with no N_2O. The sequence of anesthetic administration was randomly selected in each animal.

The number of dogs in which VAE was detected by a given monitoring modality was compared in the presence and absence of N_2O at each air infusion rate using the Fisher's exact test. To allow a statistical comparison of a given monitor's sensitivity in detecting VAE in both the presence and absence of N_2O, the mean quantity of infused air necessary to elicit a positive response in both the presence and absence of N_2O was calculated for each monitor. The mean quantity of air was calculated as the product of air infusion rate and duration of infusion at that rate (to elicit a positive response) and did not include previous infusions of air at other rates in the same dog. Student's paired *t* test was used for intragroup comparisons, *i.e.*, 50% N_2O compared to 100% O_2 and 75% N_2O compared to 100% O_2. A two-sample unpaired *t* test was used for intergroup comparisons, *i.e.*, 75% N_2O compared to 50% N_2O. Differences were considered statistically significant at $P < 0.05$.

TABLE 1. Number of Dogs with Positive Response: Group 1

Venous Air Infusion Rate ($ml \cdot kg^{-1} \cdot min^{-1}$)	Monitoring Method and Positive Test Criteria							
	Transesophageal Echocardiography (n = 6)		Precordial Doppler Ultrasound (n = 7)		↓ PET_{CO_2} ≥ 2 mmHg (n = 7)		↑ PAP ≥ 3 mmHg (n = 7)	
	100% O_2	50% N_2O	100% O_2	50% N_2O	100% O_2	50% N_2O	100% O_2	50% N_2O
0.005	4	4	3	4	1	2	0	0
0.01	5	6	6	6	2	5	0	1
All rates > 0.01	6	6	7	7	7	7	7	7

PART 2

The purpose of the second part of this study was to determine the volume of VAE necessary to produce hypotension during anesthesia with isoflurane compared to anesthesia with isoflurane and 50% N_2O when N_2O administration is discontinued immediately upon Doppler detection of VAE.

In group 3 (n = 7), venous air was infused in each animal during anesthesia with isoflurane in O_2 and during anesthesia with isoflurane and 50% N_2O in O_2. Prior to each infusion of air, isoflurane concentration was adjusted in the presence and absence of N_2O to provide a total of 1 MAC anesthetic level. Air was infused at 0.1, 0.2, 0.4, and 0.8 $ml \cdot kg^{-1} \cdot min^{-1}$ in random sequence. Real-time Doppler changes were monitored by a blinded, experienced observer (SB, DAM). ET_{CO_2}, RAP, PAP, and MAP were monitored continuously with each air infusion. Immediately upon Doppler detection of VAE, N_2O administration was discontinued when present. The inspired concentration of isoflurane was not altered. Air infusions were terminated as soon as MAP decreased by 10 mmHg or 15 min elapsed, whichever occurred first. In those dogs with a decrease in MAP of 10 mmHg or more during the air infusion, the elapsed time (seconds) of venous air infusion necessary to elicit a positive Doppler response and the volume of air (milliliters per kilogram) were recorded. In these dogs, maximal changes in MAP, PAP, RAP, and ET_{CO_2} with each infusion of air were also recorded. Means were calculated for the elapsed time to elicit a positive Doppler response, volume of air to decrease MAP by 10 mmHg, and maximal changes in MAP, PAP, RAP, and ET_{CO_2} in both the presence and absence of N_2O. Intragroup comparisons were made for each of these variables using Student's paired *t* test. Differences were considered statistically significant at $P < 0.05$.

Following completion of the experimental protocol, monitoring devices and catheters were removed. Neuromuscular blockade was reversed with neostigmine and glycopyrrolate. Animals were allowed to emerge from general anesthesia, and their tracheas were extubated. Animals were returned to the animal care facility, where they received food and water *ad libitum.*

Results

The air infusion rates at which the different monitors for VAE elicited a positive response in the presence of 50 and 75% N_2O compared to 100% O_2 are shown in tables 1 and 2. There were no significant differences between 100% O_2 and 50% N_2O in the group 1 dogs. However, in the group 2 dogs, 75% N_2O resulted in a significant increase in positive responses for ET_{CO_2} at an infusion rate of 0.005 $ml \cdot kg^{-1} \cdot min^{-1}$ and for PAP at an infusion rate of 0.01 $ml \cdot kg^{-1} \cdot min^{-1}$.

The mean quantity of air to elicit a positive response for each monitor in the presence and absence of N_2O is shown in table 3. In group 1 animals, there was no significant difference in the volume of air necessary to elicit a positive response with the TEE or Doppler (0.05 ml/kg for each) in the presence of 50% N_2O compared to 100% O_2. However, changes in ET_{CO_2} occurred with 0.12 ml/kg air in the presence of 50% N_2O compared to 0.15 ml/kg in the presence of 100% O_2, ($P = 0.03$) while changes in PAP occurred with 0.18 ml/kg air in the pres-

TABLE 2. Number of Dogs with Positive Response: Group 2 (n = 7)

Venous Air Infusion Rate ($ml \cdot kg^{-1} \cdot min^{-1}$)	Monitoring Method and Positive Test Criteria							
	Transesophageal Echocardiography		Precordial Doppler Ultrasound		↓ PET_{CO_2} ≥ 2 mmHg		↑ PAP ≥ 3 mmHg	
	100% O_2	75% N_2O	100% O_2	75% N_2O	100% O_2	75% N_2O	100% O_2	75% N_2O
0.005	4	5	4	5	1	5*	0	0
0.01	6	7	6	7	4	7	0	4*
All rates > 0.01	7	7	7	7	7	7	7	7

* Significantly different from 100% O_2 value ($P < 0.05$).

TABLE 3. Thresholds of Detection for Venous Air Embolism in Presence and Absence of N_2O

Monitoring Method	Mean Quantity of Air (ml/kg) to Elicit Positive Response (±SD)			
	Group 1		Group 2	
	100% O_2	50% N_2O	100% O_2	75% N_2O
Transesophageal echocardiography	0.05 ± 0.02	0.05 ± 0.02	0.06 ± 0.02	0.06 ± 0.01
Precordial Doppler ultrasound	0.05 ± 0.02	0.05 ± 0.01	0.06 ± 0.02	0.06 ± 0.01
↓ PET_{CO_2} ≥ 2 mmHg	0.15 ± 0.04	0.12 ± 0.03*	0.14 ± 0.04	0.10 ± 0.02*
↑ PAP ≥ 3 mmHg	0.27 ± 0.06	0.18 ± 0.04*	0.27 ± 0.03	0.12 ± 0.02*†

* $P < 0.05$ as compared to 100% O_2.

† $P < 0.05$ as compared to 50% N_2O.

ence of 50% N_2O compared to 0.27 ml/kg in the presence of 100% O_2 ($P = 0.01$) (table 3). In group 2 animals, there was again no significant difference in the volume of air necessary to elicit a positive response with the TEE or Doppler (0.06 ml/kg for each) in the presence of 75% N_2O compared to 100% O_2. However, changes in ET_{CO_2} occurred with 0.10 ml/kg in the presence of 75% N_2O compared with 0.14 ml/kg in the presence of 100% O_2 ($P = 0.02$), while changes in PAP occurred with 0.12 ml/kg in the presence of 75% N_2O compared with 0.27 ml/kg in the presence of 100% O_2 ($P < 0.001$) (table 3).

In group 3 animals, the only intragroup differences in baseline variables, *i.e.*, prior to the infusion of air, were those related to the anesthetic state (table 4). There was no statistically significant difference in the percentage of animals in which MAP decreased by 10 mmHg or more during any air infusion rate studied when dogs were initially anesthetized with isoflurane and 50% N_2O compared to isoflurane alone (table 5). When administration of 50% N_2O was discontinued immediately upon Doppler detection of VAE, N_2O did not influence either the volume of air required to decrease the MAP by 10 mmHg or the maximum changes in MAP, PAP, RAP, and ET_{CO_2} associated with that volume of infused air (table 6).

Discussion

Early detection and prompt treatment of VAE are recognized important factors that can limit morbidity and mortality.[6] Because N_2O is known to enlarge air-containing cavities in the body, it is possible that the use of N_2O will allow earlier detection of VAE, *i.e.*, detection of smaller quantities of entrained air, by enlarging intravascular gas volumes. Our results indicate that the detection of VAE by the most sensitive monitors, *i.e.*, the precordial Doppler and TEE, is unaffected by N_2O. As commonly used in the clinical setting to detect VAE, the precordial Doppler and TEE are qualitative monitors for VAE. As such, they are not responsive to changes in intravascular air volume. They detect only the presence or absence of intravascular air rather than quantify the amount of air present. As generated in the dog model examined in this study, bubble size in the absence of N_2O must have been greater than the "critical" size necessary for detection by these two devices. Therefore, any increase in bubble size secondary to N_2O was of no consequence in detection of VAE. Thus, even at the lowest air infusion rate studied (0.005 $ml \cdot kg^{-1} \cdot min^{-1}$), there was no statistically significant difference in the number of dogs in whom VAE was detected by TEE or Doppler in the presence and absence of N_2O (tables 1 and 2). The possibility of a type II statistical error exists due to the small number of animals studied.

In contrast to the TEE and Doppler, ET_{CO_2} and PAP monitoring are semiquantitative monitors for VAE. As demonstrated by others, the magnitude of change in ET_{CO_2} and PAP following VAE correlates with the volume of air infused.[4] As monitors for VAE that are responsive to changes in intravascular air volume, changes in ET_{CO_2} and PAP would be expected to occur with lower volumes of infused air in the presence of N_2O due to expansion of the intravascular gas by N_2O. This was observed in our dog model of VAE. Theoretically, the vol-

TABLE 4. Baseline Parameters in Group 3 Dogs (mean ± SD)

Parameter	Anesthetic	
	Isoflurane + O_2	Isoflurane + O_2 + 50% N_2O
ETISO (%)	1.48 ± 0.02	1.10 ± 0.02*
ETN_2O (%)	0.7 ± 0.4	50.4 ± 0.8*
Temperature (° C)	36.8 ± 0.2	36.9 ± 0.2
Pa_{O_2} (mmHg)	423 ± 50	212 ± 37*
Pa_{CO_2} (mmHg)	40.6 ± 2.2	39.5 ± 2.5
*p*H	7.36 ± 0.02	7.37 ± 0.03
Hemoglobin (g/dl)	12.1 ± 0.8	12.5 ± 1.1*
MAP (mmHg)	109 ± 15	119 ± 17*
PAP (mmHg)	21 ± 2	22 ± 2*
RAP (mmHg)	5 ± 1	5 ± 1
Heart rate (beats/min)	134 ± 22	149 ± 22*
PET_{CO_2} (mmHg)	34 ± 2	33 ± 3

Includes only air infusions for which MAP decreased by ≥10 mmHg in both the 50% N_2O and 100% O_2 states (n = 19 infusions).

ET_{ISO} = end-tidal isoflurane tension; ET_{N_2O} = end-tidal N_2O tension; MAP = mean arterial pressure; PAP = pulmonary artery pressure; RAP = right atrial pressure; PET_{CO_2} = end-tidal CO_2 tension.

* $P < 0.05$ compared to isoflurane + O_2.

ume of an air-containing cavity can increase to 200% and 400% of its original volume in the presence of 50% and 75% N_2O, respectively. Based on this volume expansion, we would predict a 50% and 75% reduction in the volume of infused air necessary to produce a given change in ET_{CO_2} and PAP in the presence of 50% and 75% N_2O, respectively, compared to the volume required in the presence of 100% O_2. Although we observed a reduction in the volume of air necessary to produce a given change in ET_{CO_2} and PAP in the presence of 50% and 75% N_2O as compared to the presence of 100% O_2, the reduction was not of the predicted magnitude. This probably reflects the semiquantitative nature of these measurements in relation to air volume.

As shown in table 3, the mean quantity of air to elicit a positive response with ET_{CO_2} monitoring was significantly less in the presence of 50% N_2O compared to 100% O_2. However, as shown in table 1, at an air infusion rate of 0.01 $ml \cdot kg^{-1} \cdot min^{-1}$, the number of dogs in which ET_{CO_2} decreased by 2 mmHg or more in the presence and absence of 50% N_2O (5 of 7 *vs.* 2 of 7, respectively) was not significantly different. These two observations together suggest that the failure to detect a statistical difference at this infusion rate might be due to the small number of animals that were studied. The possibility of a type II statistical error exists.

Munson and Merrick[3] have shown that when air is injected as an intravenous bolus in rabbits anesthetized with halothane and N_2O in O_2 and administration of N_2O is continued following air injection, the lethal dose of injected air is decreased in the presence of 75% N_2O as compared to 100% O_2.[3] This differs from the clinical situation, in which a patient—for example, a neurosurgical patient undergoing a craniectomy in the sitting position—is being monitored for VAE with highly sensitive monitors such as the precordial Doppler and/or TEE. In this situation, N_2O administration is routinely discontinued immediately upon Doppler detection of VAE. The second part of our study attempted to mimic this clinical situation. In contrast to the methodology of Munson and Merrick, our study evaluated the hemodynamic response to air administered by continuous intravenous infusion when N_2O is discontinued immediately upon Doppler detection of VAE. Under these circumstances, the volume of air necessary to decrease the MAP by 10 mmHg and the severity of hemodynamic compromise secondary to VAE was unaffected by the initial presence of 50% N_2O. It is likely that the rapid washout of N_2O after its administration is discontinued limits volume expansion of intravascular air when VAE is detected early using the precordial Doppler. In addition, it is possible that this lack of hemodynamic effect might, to some extent, be due to a reduction in the depth of anesthesia associated with discontinuing the administration of N_2O.

In conclusion, use of N_2O does not improve the sensitivity (*i.e.*, reduce the threshold of detection of air emboli) of the TEE or precordial Doppler but does improve the sensitivity of ET_{CO_2} and PAP monitoring in the detection of VAE. In isoflurane-anesthesized dogs during continuous intravenous infusion of air at rates up to 0.8 $ml \cdot kg^{-1} \cdot min^{-1}$, hemodynamic compromise is not worsened in animals receiving 50% N_2O if N_2O administration is discontinued immediately upon Doppler detection of VAE.

TABLE 5. Number of Dogs in Group 3 Showing a Decrease in Mean Arterial Pressure ≥ 10 mmHg during Venous Air Infusion (n = 7)

Infusion Rate of Air ($ml \cdot kg^{-1} \cdot min^{-1}$)	Anesthetic	
	Isoflurane + O_2	Isoflurane + O_2 + 50% N_2O*
0.1	4	2
0.2	5	5
0.4	7	7
0.8	7	7

* N_2O discontinued immediately upon Doppler detection of VAE.

TABLE 6. Hemodynamic Changes with Venous Air Embolism during Isoflurane and Isoflurane–N_2O Anesthesia

	Isoflurane + O_2	Isoflurane + O_2 + 50% N_2O*
Elapsed time (s) to elicit positive Doppler (±SD)	23 ± 19	20 ± 14
Volume of air (ml/kg) producing ↓ MAP = 10 mmHg (±SD)	1.52 ± 0.64	1.39 ± 0.79
MAX ↓ in MAP (mmHg)	23 ± 10	24 ± 12
MAX ↑ PAP (mmHg)	18 ± 7	20 ± 10
MAX ↓ PET_{CO_2} (mmHg)	18 ± 3	17 ± 3
MAX ↑ RAP (mmHg)	2 ± 1	2 ± 2

* N_2O discontinued immediately upon Doppler detection of venous air embolism.

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