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Fifty Percent Nitrous Oxide Does Not Increase the Risk of Venous Air Embolism in Neurosurgical Patients Operated upon in the Sitting Position

Thomas J. Losasso, M.D., Donald A. Muzzi, M.D.,* Niki M. Dietz, M.D.,† Roy F. Cucchiara, M.D.‡*

Although nitrous oxide (N_2O) should theoretically increase the severity of venous air embolism (VAE), data confirming this hazard in clinical situations are not available. The effect of 50% N_2O on the incidence and severity of VAE and on the emergence time from anesthesia was evaluated in 300 neurosurgical patients operated upon while in the sitting position. Of these, 110 patients underwent craniectomy for posterior fossa pathology and 190 patients underwent cervical spine surgery (CSS). Patients were randomized to receive either 50% N_2O in oxygen (O_2) (N_2O group) or O_2 (no-N_2O group) as part of an isoflurane–fentanyl-based anesthetic. In patients in the N_2O group, N_2O administration was discontinued immediately upon Doppler-detection of VAE and was reinstituted in not less than 30 min after resolution of the episode. The incidence of Doppler-detected VAE was significantly greater in the craniectomy group than the CSS group (43% *vs.* 7%, respectively; $P < 0.001$). N_2O had no effect on the incidence of VAE or the severity of VAE as judged by the magnitude of the reduction in blood pressure during hemodynamically significant episodes of VAE, the volume of gas aspirated from the right atrial catheter during episodes of VAE, or the magnitude of the decrease in end-tidal carbon dioxide tension during episodes of VAE. Hemodynamically significant episodes of VAE (*i.e.*, episodes associated with a reduction in systolic blood pressure of ≥ 15 mmHg) occurred in 17 of the 61 patients experiencing VAE (28%) and was not different between the N_2O and no-N_2O groups. Similarly, hemodynamically significant episodes of VAE (n = 18) accounted for 15% of all episodes of VAE (n = 118) and was not different between the N_2O and no-N_2O groups. Emergence time was not significantly different between the N_2O and no-N_2O groups, with mean times of 2 ± 6 and 3 ± 7 min (± SD), respectively. Emergence time was significantly longer in the craniectomy group than in the CSS group (5 *vs.* 1 min, respectively; $P < 0.001$). Within the craniectomy group, the incidence of Doppler-detected VAE was significantly less in patients with previous surgery at the operative site (21%) compared to patients without previous surgery at the operative site (47%). Postoperatively, no complications could be related to the use of N_2O or directly attributed to the occurrence of VAE. The authors conclude that in neurosurgical patients operated upon while in the sitting position, 50% N_2O has no measurable effect on the incidence or severity of VAE if its administration is discontinued immediately upon Doppler detection of VAE. In addition, when the anesthetic agents are administered so as to have the patient awake at the completion of surgery, use of 50% N_2O to supplement an isoflurane–fentanyl-based anesthetic has no measurable effect on the emergence time from anesthesia. (Key words: Anesthesia: neurosurgical. Anesthetics, gases: nitrous oxide. Complications: venous air embolism. Position: sitting.)

VENOUS AIR EMBOLISM (VAE) is a well-recognized complication in patients undergoing neurosurgical procedures in the sitting position.[1–4] Previous studies indicate that the incidence of Doppler-detected VAE ranges between 11 and 24% during cervical spine surgery (CSS) and between 41 and 45% during craniectomy in patients in the sitting position.[1–4]

Because of the difference in blood–gas solubility between nitrous oxide (N_2O) and nitrogen (N_2), N_2O will enlarge the gas volume of air-containing cavities such as intravascular air bubbles.[5–7] Volume expansion of intravascular air bubbles may increase the risk of hemodynamic compromise or other morbidity after the occurrence of VAE. In a rabbit model of VAE, Munson and Merrick found that the lethal volume of intravenously administered air was significantly less in animals receiving N_2O compared to animals not receiving N_2O.[8] These authors suggested that "until a more complete evaluation of the incidence and severity of VAE during nitrous oxide anesthesia can be made, we believe it is best avoided in patients in whom the risk of air embolism is great."[9] Alternatively, it is theoretically possible that this volume expansion may allow for earlier detection and, consequently, prompter treatment of VAE. Based on these considerations, use of N_2O in sitting neurosurgical patients is considered controversial.

A second issue relates to the effect of N_2O on emergence time. Because of the lower blood–gas solubility and therefore more rapid washout of N_2O compared to isoflurane, it is possible that this difference facilitates a more rapid emergence from anesthesia in patients receiving N_2O.

We performed a prospective, randomized study in neurosurgical patients operated upon while in the sitting position to determine 1) if the incidence and severity of VAE are affected by 50% N_2O when its administration is discontinued immediately upon Doppler detection of VAE and 2) whether emergence times after neurosurgery differ in patients anesthetized with and without 50% N_2O to supplement an isoflurane–fentanyl-based anesthetic.

* Assistant Professor of Anesthesiology, Mayo Clinic.

† Resident in Anesthesiology, Mayo Clinic.

‡ Professor of Anesthesiology, University of Florida College of Medicine.

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Address reprint requests to Dr. Losasso: Department of Anesthesiology, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905.

Materials and Methods

With Institutional Review Board approval, 190 patients undergoing CSS and 110 patients undergoing craniectomy in the sitting position were studied over a 2-yr period. Informed consent was obtained from patients or family members. Patients were randomly assigned to receive either 50% N_2O in oxygen (O_2) (N_2O group) or O_2 (no-N_2O group) as part of an anesthetic that included isoflurane and fentanyl. Because the incidence of VAE is known to be different between patients undergoing CSS and those undergoing craniectomy in the sitting position,[2] patients in the two surgical groups were randomized separately.

Patients with the following conditions were excluded from study: presence of a pneumothorax or bullae on preoperative chest x-ray, craniotomy within 10 days prior to surgery, New York Heart Association class 3–4 angina, cardiopulmonary disease with a known right-to-left intracardiac shunt, and/or respiratory disease necessitating the use of an inspired O_2 fraction > 0.5 or positive end-expiratory pressure. In addition, patients requiring emergency surgery and patients 12 yr of age or younger were excluded from this study.

Anesthesia was induced with thiopental. Vecuronium or succinylcholine was administered to facilitate laryngoscopy and tracheal intubation. The lungs were mechanically ventilated. Anesthesia was maintained with isoflurane and fentanyl, with or without 50% N_2O in O_2. Neuromuscular blockade was maintained throughout the surgical procedure with a nondepolarizing muscle relaxant except in cases using intraoperative electromyographic monitoring. The dose of fentanyl and concentration of isoflurane administered were determined by the anesthesiologist. Fentanyl was not administered during the final 30 min of the neurosurgical procedure.

Intraoperative monitoring included a five-lead electrocardiogram, blood pressure cuff, esophageal stethoscope, pulse oximeter, peripheral nerve stimulator, indwelling radial artery catheter, multiorifice right atrial (RA) catheter (kit AK-04250, Arrow Catheter Company), precordial Doppler ultrasound, and mass spectrometer. After the patient was placed in the sitting position, satisfactory RA catheter tip location was determined using an electrocardiogram trace from the catheter. Correct placement of the precordial Doppler was presumed when 10 ml agitated saline injected through the RA catheter elicited a characteristic change in Doppler sounds. With the patient in the sitting position, the arterial pressure transducer was zeroed to the base of the skull.

Precordial Doppler sounds were monitored continuously throughout the surgical procedure. A distinct change from the normal sound was considered evidence of VAE and in all cases was confirmed by an experienced neuroanesthesiologist. Immediately upon Doppler detection of VAE, the neurosurgeon was notified; surgical efforts aimed at limiting air entrainment were instituted; the RA catheter was aspirated; and in patients receiving N_2O, its administration was discontinued. Jugular vein compression was instituted at the discretion of the neuroanesthesiologist and neurosurgeon. In patients with a decrease in systolic blood pressure of 15 mmHg or more after the occurrence of VAE, at the discretion of the neuroanesthesiologist, vasopressors and/or antiarrhythmic agents were administered and/or the head of the operating table was temporarily lowered. In patients randomized to the N_2O group, N_2O administration was reinstituted not less than 30 min after the resolution of an episode of VAE (resolution was defined as return of the Doppler sounds to normal).

The severity of each episode of VAE was graded according to the following scoring system: grade 1 = Doppler changes with or without aspiration of gas from the RA catheter; grade 2 = Doppler changes and a decrease in end-tidal carbon dioxide tension (PET_{CO_2}) ≥ 2 mmHg; grade 3 = Doppler changes and a decrease in systolic blood pressure ≥ 15 mmHg; grade 4 = Doppler changes followed by electromechanical dissociation or cardiac arrest. The volume of gas aspirated from the RA catheter was estimated during each episode of VAE as either none, small (less than 5 ml), medium (5–20 ml), or large (greater than 20 ml).

For patients who were to be awakened and undergo tracheal extubation in the operating room at the completion of surgery, the anesthetic agents were administered so as to have the patient awake (*i.e.*, opening eyes and moving extremities to command) when the patient was returned to the supine position with the surgical dressing in place. The elapsed time, in minutes, from the return of the patient to the supine position with the surgical dressing in place until the patient was awake was defined as the emergence time. Emergence time was recorded as 0 min for patients who were awake before surgical dressing placement was complete. At the discretion of the anesthesiologist, naloxone was administered, in 40-μg increments, to patients who were unresponsive to command despite end-tidal isoflurane and N_2O concentrations less than 1.0 mmHg and 5%, respectively. Emergence was considered delayed for patients with emergence times of greater than 10 min.

In patients in the N_2O group, N_2O administration was reinstituted not less than 30 min after an episode of VAE. A subsequent episode of VAE that was detected while the patient was not receiving N_2O is hereafter termed a crossover episode (*i.e.*, a no-N_2O episode in a patient randomized to the N_2O group). The severity of the episodes of

VAE, estimated volume of retrievable gas from the RA catheter, and reductions in PET_{CO_2} were compared both between groups (N_2O *vs.* no-N_2O group) and between episodes (N_2O *vs.* no-N_2O episodes). Data from the crossover episodes were included in the N_2O group data when group comparisons were made and were included as no-N_2O episode data when episode comparisons were made.

In patients in the N_2O group experiencing VAE who were undergoing craniectomy, N_2O administration was not reinstituted after completion of dural closure if it was not being administered during dural closure. Anesthesia was conducted in this fashion based upon our usual clinical practice and unresolved issues concerning the development of tension pneumocephalus.[10–12] For patients who experienced VAE, hospital records for the first 24-h period postoperatively were reviewed in a retrospective fashion to identify any morbidity or mortality that might have been related to VAE.

Using Student's *t* test for unpaired data, comparisons were made for age, height, weight, duration of surgical procedure, duration of anesthesia, emergence time, dose of fentanyl, average end-tidal isoflurane concentration during the surgical procedure, magnitude of the reduction in systolic blood pressure during hemodynamically significant episodes of VAE, maximal reduction in PET_{CO_2} during episodes of VAE, and the duration of episodes of VAE. The incidence of Doppler-detected VAE and incidence of hemodynamically significant episodes of VAE (grade-3 or -4 episodes) were compared between the N_2O and no-N_2O groups using the chi-square test. The severity of the episodes of VAE and estimated volume of retrievable gas from the RA catheter during episodes of VAE were compared both between groups and between episodes (N_2O *vs.* no-N_2O) using the Mann-Whitney rank sum test. The incidence of delayed emergence and naloxone administration was compared between groups using Fisher's exact test. Differences were considered significant at $P < 0.05$.

TABLE 1. Surgical Procedure and Indication for Surgery

	N_2O Group (n = 150)	No-N_2O Group (n = 150)
Suboccipital craniectomy	55	55
Tumor resection	36	39
Resection of ateriovenous malformation	2	5
Aneurysm clipping	2	3
Arnold-Chiari malformation	11	4
Other	4	4
Cervical spine surgery	95	95
Disc extrusion	47	58
Spinal stenosis	20	5
Osteophye, foraminal disease, spondylosis	16	17
Other	12	15
Total	150	150

TABLE 2. Patient Demographic Characteristics

	N_2O Group	No-N_2O Group
n	150	150
Age (yr)		
Mean ± SD	50 ± 15	51 ± 16
Range	14–84	14–82
Males (n)	89	95
Females (n)	61	55
Male:female	1.5:1	1.7:1
Height (cm)	169 ± 19	169 ± 10
Weight (kg)	78 ± 17	75 ± 16

Values are mean ± SD.

Results

Table 1 lists the indications for surgery. Table 2 indicates the demographic data for patients in the N_2O and no-N_2O groups.

In patients undergoing CSS, Doppler-detected VAE occurred in 7 of 95 patients (7%) in the N_2O group compared to 7 of 95 patients (7%) in the no-N_2O group (P = no significant difference [NS]). In patients undergoing craniectomy, Doppler-detected VAE occurred in 24 of 55 patients (44%) in the N_2O group compared to 23 of 55 patients (42%) in the no-N_2O group (P = NS). However, the incidence of Doppler-detected VAE was significantly greater in the craniectomy than in the CSS group ($P < 0.001$).

A total of 118 episodes of Doppler-detected VAE were identified in this study: 64 episodes occurred in patients in the N_2O group, and 54 episodes occurred in patients in the no-N_2O group (P = NS). Of the 64 episodes that occurred in the N_2O group, 52 were N_2O episodes, and 12 were crossover episodes.

There was no statistically significant difference in the incidence of hemodynamically significant VAE between the N_2O and no-N_2O groups. In patients experiencing one or more episodes of Doppler-detected VAE, the VAE was hemodynamically significant in 8 of 31 patients (26%) in the N_2O group compared to 9 of 30 patients (30%) in the no-N_2O group (P = N.S).

There was no statistically significant difference in the severity of episodes of VAE between the N_2O and no-N_2O groups (fig. 1). Figure 1 shows the distribution of episodes of VAE among the four grades for patients in the N_2O and no-N_2O groups. The majority of episodes of VAE were hemodynamically insignificant, *i.e.*, grade 1 or 2, in each group. There were nine episodes of hemodynamically significant VAE in each of the N_2O and no-N_2O groups. Of the nine episodes in the N_2O group, three were crossover episodes. There were no grade-4 episodes of VAE in either the N_2O or no-N_2O groups. In addition,

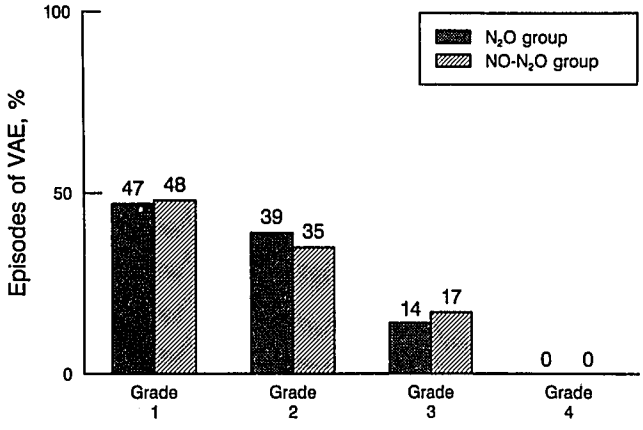

FIG. 1. Severity of venous air embolism (VAE) in the N_2O and No-N_2O groups. The relative distribution of episodes amongst the four grades is not significantly different between the N_2O and No-N_2O groups. (Grade 1 = Doppler changes with or without aspiration of gas from the right atrial catheter; grade 2 = Doppler changes + decrease in $PET_{CO_2} \geq 2$ mmHg; grade 3 = Doppler changes + decrease in systolic blood pressure ≥ 15 mmHg; grade 4 = Doppler changes followed by electromechanical dissociation or cardiac arrest. N_2O group includes crossover episodes.)

there was no statistically significant difference in the severity of the N_2O and no-N_2O episodes of VAE (Fig. 2).

There was no statistically significant difference between the N_2O and no-N_2O groups in the magnitude of the reduction in systolic blood pressure during hemodynamically significant episodes of VAE. In the N_2O group, one hemodynamically significant episode occurred in each of seven patients and two episodes occurred in one patient, whereas in the no-N_2O group, one hemodynamically significant episode occurred in each of nine patients (table 3). In the N_2O group, the reduction in systolic blood pressure during hemodynamically significant episodes of VAE was 35 ± 26 mmHg (mean ± SD) with a range of 16–86 mmHg, compared to the no-N_2O group, in which the reduction in systolic blood pressure was 34 ± 16 mmHg with a range of 15–58 mmHg. In addition, there was no difference in the magnitude of the reduction in systolic blood pressure between hemodynamically significant N_2O and no-N_2O episodes of VAE (34 ± 28 and 35 ± 17 mmHg, respectively).

There was no difference in the estimated volume of retrievable gas from the RA catheter during episodes of VAE between the N_2O and no-N_2O groups (fig. 3) or between the N_2O and no-N_2O episodes (fig. 4). In addition, there was no difference in the magnitude of the reduction in PET_{CO_2} during episodes of VAE between the N_2O and no-N_2O groups (3.0 ± 2.9 and 3.1 ± 3.5 mmHg, respectively) or between the N_2O and the no-N_2O episodes of VAE (2.7 ± 2.6 mmHg and 3.4 ± 3.6 mmHg, respectively). The duration of the episodes of VAE was not different between the N_2O and no-N_2O groups (14 ± 26 and 10 ± 10 min, respectively). Similarly, the duration of the episodes of VAE was not different between the N_2O and no-N_2O episodes (13 ± 27 and 12 ± 13 min, respectively).

Tables 4 and 5 indicate anesthetic and surgical variables for patients in whom an emergence time was available. Emergence time was not available in 20 patients. Reasons for this included the following: computed tomography scan or angiogram to be obtained immediately postoperatively with the patient anesthetized; additional surgical procedure(s) to be performed after completion of the craniectomy or CSS with the patient anesthetized; inability to follow commands preoperatively due to an altered level of consciousness; a language barrier between the anesthesia team and patient; and requirements in some patients for the trachea to remain intubated and for sedation to continue postoperatively. In addition, in one patient in the no-N_2O group, cerebellar herniation occurred intraoperatively for unclear reasons. This patient did not emerge from general anesthesia and remained in a persistent vegetative state postoperatively.

There was no difference in the mean emergence time for patients in the N_2O and no-N_2O groups. The mean emergence time for the N_2O and no-N_2O groups were 2 ± 6 and 3 ± 7 min (± SD), respectively (P = NS). Emergence time was significantly greater in the craniectomy group compared to the CSS group. The mean emergence time for the craniectomy and CSS groups was 5 ± 10 and 1 ± 2 min, respectively ($P < 0.001$ by Student's unpaired

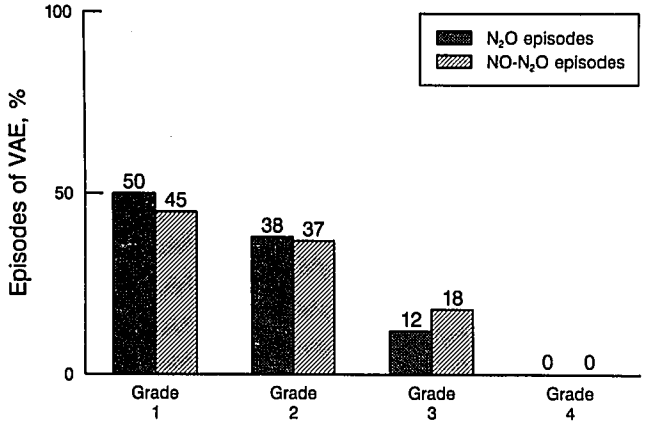

FIG. 2. Severity of venous air embolism (VAE) for N_2O and No-N_2O episodes. The relative distribution of episodes among the four grades is not significantly different between the N_2O and No-N_2O episodes. (Grades are defined as in fig. 1. No-N_2O episodes include crossover episodes.)

TABLE 3. Patients with Hemodynamically Significant Venous Air Embolism

Patient	Procedure	Baseline ET_{N_2O}* (%)	Baseline SBP† (mmHg)	Maximum Decrease in SBP (mmHg)	Dysrhythmias	Vasopressor/ Antiarrhythmic	Temporarily Lowered Head of Bed
N_2O Group							
1	CRAN	49	100	18	None	None	No
2‡	CRAN	2	135	67	None	Mephentermine	No
3‡	CRAN	3	145	20	None	None	No
4	CRAN	47	115	16	None	None	No
5	CRAN	49	123	20	None	None	No
5‡	CRAN	2	106	26	Bigeminy/bradycardia	Atropine/lidocaine	Yes
6	CRAN	50	120	86	None	Ephedrine	No
7	CRAN	47	106	18	None	None	No
8	CSS	49	106	46	None	None	Yes
No-N_2O Group							
9	CRAN	—	130	40	PACs	None	No
10	CRAN	—	120	26	None	None	No
11	CRAN	—	128	20	None	None	Yes
12	CRAN	—	168	58	None	Ephedrine	No
13	CRAN	—	110	15	None	None	No
14	CRAN	—	122	20	None	None	No
15	CRAN	—	140	36	PVCs	None	No
16	CSS	—	144	57	None	None	Yes
17	CSS	—	122	38	None	Mephentermine	No

CRAN = craniectomy; CSS = cervical spine surgery.

* End-tidal N_2O (ET_{N_2O}) when venous air embolism first detected by Doppler.

† Systolic blood pressure (SBP) when venous air embolism first detected by Doppler.

‡ Crossover episodes.

t test). In addition, delayed emergence occurred with greater frequency in the craniectomy group than the CSS group: 12% *versus* 1%, respectively ($P < 0.001$ by Fisher's exact test; fig. 5).

Within the craniectomy group, the incidence of Doppler-detected VAE was different in patients with and without previous surgery at the operative site. Doppler-detected VAE occurred in 4 of 19 patients (21%) with previous surgery at the operative site compared to 43 of 91 patients (47%) without previous surgery at the operative site ($P = 0.03$). In patients undergoing CSS, there was no difference in the incidence of Doppler-detected VAE between patients with and without previous surgery at the operative site.

No complications were identified postoperatively that could be attributed directly to the intraoperative occurrence of VAE, nor was there any mortality related to VAE in this series of patients. However, two patients in the N_2O and one patient in the no-N_2O group experienced pulmonary complications that may have been related to venous air entrainment. In each case, the respiratory dysfunction was effectively treated with pharmacologic intervention (morphine and/or furosemide) and/or transient ventilatory support.

Tension pneumocephalus was diagnosed in the immediate postoperative period in one patient. This patient, a 38-yr-old woman who underwent a suboccipital craniectomy for resection of a pinealoblastoma, did not receive N_2O. Postoperatively, the patient displayed an unexpected, severely decreased level of consciousness. A brow-up, lateral skull roentgenogram revealed a large bifrontal pneumocephalus. The diagnosis of tension pneumoce-

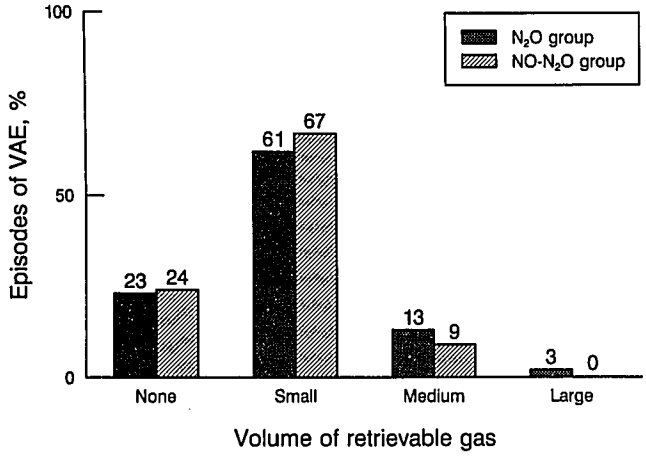

FIG. 3. Estimated volume of retrievable gas from the right atrial catheter during episodes of venous air embolism (VAE) in the N_2O and No-N_2O groups. The relative frequency with which the different volumes of gas were aspirated was not different between the N_2O and No-N_2O groups. (Small = <5 ml, medium = 5–20 ml, and large = >20 ml. N_2O group includes crossover episodes.)

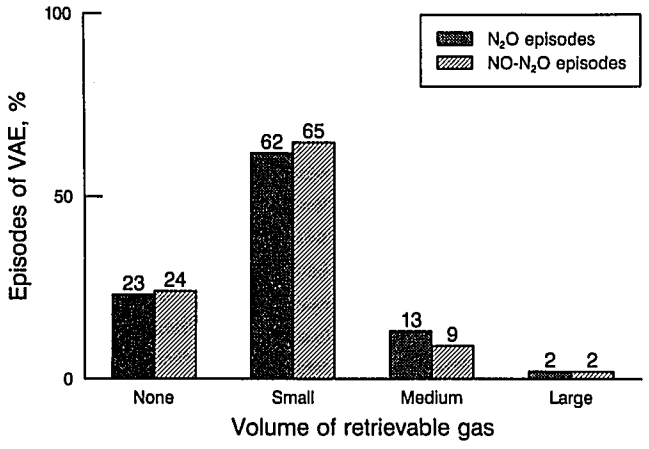

FIG. 4. Estimated volume of retrievable gas from the right atrial catheter during N_2O and No-N_2O episodes of VAE. The relative frequency with which the different volumes of gas were aspirated was not different between the N_2O and No-N_2O episodes. (Volumes are defined as in fig. 3. No-N_2O episodes include crossover episodes.)

phalus was confirmed after intracranial air was released using a twist-drill burr hole and 18-G needle to penetrate the dura over the right frontal region. The patient's level of consciousness improved after this intervention.

Discussion

The risks and benefits of using N_2O in patients undergoing surgery while in the sitting position have been an issue of debate.[7,8,13,14] Arguments in favor of the use of N_2O are based on the theoretical consideration that entrained air will expand rapidly, allowing earlier detection of VAE and prompter surgical intervention to identify and control the site of air entrainment. However, there are no clinical or laboratory data to support this concept.

TABLE 4. Variables Associated with Anesthesia and Surgery

	N_2O Group	No-N_2O Group
Total patients (n)	142	138
CRAN (n)	50	47
CSS (n)	92	91
Duration of surgical procedure (min)	211 ± 97	211 ± 103
Duration of anesthesia (min)	276 ± 113	277 ± 119
Fentanyl dose (μg/kg)	5.6 ± 3.3	6.3 ± 3.4
Average ETISO (%)	0.52 ± 0.20	0.65 ± 0.18*
Patients receiving naloxone (n)	5	7
Emergence time (min)	2 ± 6	3 ± 7

CRAN = craniectomy; CSS = cervical spine surgery.
Values are mean ± SD. Includes only patients in whom emergence times were available.
* $P < 0.001$ compared to N_2O group.

TABLE 5. Variables Associated with Anesthesia and Surgery†

	CRAN	CSS
n	97	183
Duration of surgical procedure (min)	291 ± 90	169 ± 77*
Duration of anesthesia (min)	365 ± 105	229 ± 92*
Fentanyl dose (μg/kg)	6.8 ± 3.8	5.6 ± 3.1†
Average ETISO (%)	0.69 ± 0.19	0.53 ± 0.18*
Patients receiving naloxone (n)	10	2*
Emergence time (min) (range)	5 ± 10 (0–50)	1 ± 2* (0–13)

CRAN = craniectomy; CSS = cervical spine surgery.
Values are mean ± SD. Includes only patients in whom emergence times were available.
* $P < 0.001$ compared to CRAN group.
† $P < 0.005$ compared to CRAN group.

In fact, in a canine model of VAE, N_2O was found to have no effect on the sensitivity of either the precordial Doppler or transesophageal echocardiogram to detect VAE.[15] In addition, the use of N_2O may allow one to use a lower concentration of the more potent volatile anesthetic agents, thus facilitating an earlier emergence and neurologic evaluation after surgery. The primary argument in opposition to the use of N_2O is that entrained air will increase in volume as it passes into the venous circulation where N_2O is present, thereby producing more depressive hemodynamic consequences and increasing the morbidity and mortality from VAE.

This study was designed to address these clinical con-

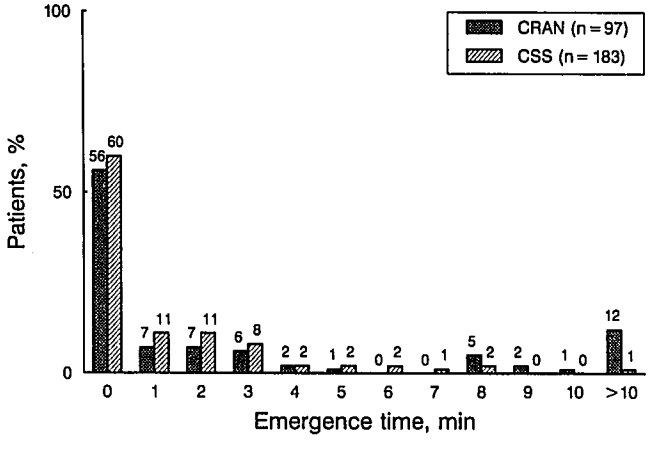

FIG. 5. Emergence time in patients undergoing craniectomy (CRAN) and cervical spine surgery (CSS). Shown is the distribution of emergence times for each surgical group. The mean emergence time was greater in the CRAN than CSS group ($P < 0.001$ by Student's t test for unpaired data). Delayed emergence occurred in 12% of the patients in the CRAN group compared to 1% of the patients in the CSS group ($P < 0.001$ by the Fisher's exact test).

siderations and to quantify the consequences of using N_2O during sitting neurosurgical procedures. Inherent in such a study is the situation in which a patient randomized to receive N_2O sustains an episode of VAE; the N_2O is discontinued immediately upon Doppler detection of VAE, as is done during routine clinical practice; and then the patient experiences an additional episode of VAE prior to having N_2O administration reinstituted. In an effort to make data analysis complete, data from these "crossover" episodes were included in the N_2O group data when group comparisons were made and in the no-N_2O episode data when episode comparisons were made so that the reader can assess the impact of these occurrences. Statistically and clinically, no differences between the N_2O and no-N_2O groups or between the N_2O and no-N_2O episodes were demonstrable because of these crossovers, and the impact on the overall results is inconsequential.

The administration of 50% N_2O to supplement general anesthesia with isoflurane and fentanyl did not increase the incidence of Doppler-detected VAE during craniectomy and CSS in patients in the sitting position. The incidence of Doppler-detected VAE in our study is consistent with that reported in several large, retrospective series reporting on VAE during neurosurgical procedures performed in the sitting position.[1–4] In these series, monitoring for VAE included the use of a precordial Doppler in the majority of patients and, with the exception of the series reported by Matjasko *et al.*,[2] N_2O was used to supplement general anesthesia in most patients. As reported in these large series, the incidence of Doppler-detected VAE is approximately 8% during cervical foraminotomy, 13–24% during cervical laminectomy, and 41–45% during posterior fossa exploration. These values are similar to the 7% incidence observed in patients undergoing CSS and the 43% incidence observed in patients undergoing craniectomy in our study.

The incidence of hemodynamically significant VAE and the magnitude of the reduction in systolic blood pressure during these hemodynamically significant episodes was not different between the N_2O and no-N_2O groups or between the N_2O and no-N_2O episodes. Table 3 shows that some patients in both groups sustained a substantial decrease in blood pressure. In all cases, these episodes were transient and were treated effectively with vasopressors and/or a temporary change in position of the head of the operating table when deemed necessary by the anesthesiologist. Although these events are of substantial concern when they occur, the mean reduction in blood pressure was not different between groups and did not result in any morbidity or mortality in this study.

Hemodynamically significant VAE, as defined in our study, occurred in 28% of the patients who experienced one or more episodes of Doppler-detected VAE. In addition, as shown in figures 1 and 2, hemodynamically significant episodes accounted for only approximately 15% of all episodes of VAE. This is consistent with the data available from several other large retrospective series. In the series reported by Black *et al.*[1] and by Young *et al.*,[4] 50–70% N_2O was used to supplement general anesthesia in most cases. Hemodynamically significant VAE was defined as a 20% or greater reduction in systolic blood pressure and/or arrhythmias by Black *et al.* and as a 10-mmHg or more reduction in blood pressure by Young *et al.* In patients experiencing VAE, it was hemodynamically significant in approximately 18% of the patients in each of these studies.

Similar to the findings from our study, in a retrospective review of 554 neurosurgical procedures performed in the sitting position, Matjasko *et al.* observed that N_2O did not appear to increase the incidence or severity of VAE.[2] In that study, for unspecified reasons, approximately 23% of the patients received 60–70% N_2O, while 75% of the patients did not receive N_2O during the operative procedure. The incidence of VAE was not different between these two groups (approximately 23%). Episodes of VAE were hemodynamically significant (defined as episodes associated with "hypotension or arrhythmia") 19% of the time in patients receiving N_2O compared to 27% of the time in patients not receiving N_2O. This difference was not statistically significant ($P > 0.25$ by chi-square analysis). Although the observations made by Matjasko *et al.* suggest that N_2O does not increase the incidence or severity of VAE, it must be pointed out that the relative number of patients undergoing CSS and posterior fossa exploration in each of the N_2O and no-N_2O groups was not specified, monitoring for VAE was not standardized, and the criteria, if any existed, according to which patients either received or did not receive N_2O were not indicated.

In the current study, an attempt was made to quantify the volume of the air (which, in the case of N_2O episodes, might be referred to more specifically as an air-containing volume) within the venous circulation during each episode of VAE. This was done by estimating the volume of retrievable gas from the RA catheter as well as by measuring the maximal reduction in PET_{CO_2} associated with each episode of VAE. In a canine model of VAE, Glenski *et al.* demonstrated a correlation between the magnitude of the reduction in PET_{CO_2} and the volume of air infused into the venous circulation.[16] These two measures were taken as separate estimates of the volume of gas within the venous system during episodes of VAE. Using these estimates, we were unable to demonstrate a volume-expanding effect of N_2O on the amount of air entrained into the venous circulation.

In a rabbit model of VAE, Munson and Merrick demonstrated that when air is injected as an intravenous bolus and N_2O administration is continued thereafter, the lethal dose of air is significantly less in animals receiving N_2O compared to those not receiving N_2O.[8] However, this experimental design is unlike standard anesthetic practice for sitting neurosurgical patients. Clinically, these patients are monitored routinely for VAE with a precordial Doppler, and upon Doppler-detection of VAE, the administration of N_2O is immediately discontinued and the lungs are ventilated with O_2. In a canine model of VAE that attempted to mimic this clinical situation, Losasso *et al.* evaluated the hemodynamic response to air administered by continuous intravenous infusion when N_2O is discontinued immediately upon Doppler-detection of VAE.[15] Under these circumstances, the volume of air necessary to produce hypotension (*i.e.*, a 10-mmHg decrease in mean arterial pressure) and the magnitude of the resulting hemodynamic aberration was not different between animals initially receiving O_2 and those initially receiving 50% N_2O in O_2. The findings of this canine study are consistent with the results from our clinical study.

Although volume expansion of air-containing cavities in the body is a well-described phenomenon, the magnitude of this volume expansion depends not only on the concentration of N_2O being administered but also on the duration of the exposure to N_2O.[6-7] In our study, N_2O had no measurable effect on the incidence or severity of VAE or on the estimated volume of intravascular gas during these episodes. Because N_2O administration was discontinued immediately upon Doppler detection of VAE, volume expansion of intravascular air should not have been more than a transient phenomenon. We theorize that the high sensitivity of the precordial Doppler to detect small volumes of entrained air, coupled with the rapid washout of N_2O after its administration is discontinued, prevented volume expansion of intravascular air from becoming clinically significant or even clinically detectable.

At the completion of most neurosurgical procedures, a timely emergence is desirable to identify and treat unexpected changes in neurologic status. In the current study, the anesthesia team was able to awaken most patients in a reasonable fashion whether or not they received N_2O. There was no evidence to suggest that the use of 50% N_2O allowed a more rapid emergence at the completion of surgery. This finding is consistent with the observations of Eger *et al.*, who found no difference in patient orientation during the first 15 min postoperatively between patients anesthetized with and without N_2O to supplement isoflurane anesthesia.[17] Our findings do not suggest that the known pharmacokinetic differences[18] between isoflurane and N_2O are untrue. Rather, it demonstrates that one can account for these differences in the clinical setting and suggests that emergence may be less of a drug-dependent than an operator-dependent phenomenon. In other words, it appears that what matters is not what is used, but rather, how it is used.

The finding that emergence time was longer and that delayed emergence occurred more commonly in the craniectomy than in the CSS group is not an unexpected finding and may be related to the extent of involvement of the brain in the operative field. However, there were differences in a variety of anesthetic and surgical variables (table 5) that were likely to contribute to this finding.

Postsurgical changes and scarring might be expected to make surgical exposure and reoperation for posterior fossa surgery more difficult, resulting in an increased incidence of VAE. However, in patients in the craniectomy group we found that VAE occurred less commonly in patients undergoing reoperation than in those having surgery for the first time. This might be explained by removal or obliteration of venous structures during the previous surgical procedure. More specifically, in patients with a previous suboccipital craniectomy, a major source of venous air entrainment—namely, a portion of the skull and associated diploic veins—has been removed. In addition, other venous structures that commonly can entrain air, such as emissary veins, bridging veins, or a dural sinus, may have been obliterated at the time of the previous operation.

It should be pointed out that our study did not include patients 12 yr of age or younger. In a retrospective review by Cucchiara and Bowers, the incidence of Doppler-detected VAE was found to be similar in children and adults undergoing suboccipital craniectomy in the sitting position.[19] However, hemodynamically significant VAE occurred with greater frequency in children compared to adults (69% *vs.* 36%). Fifty percent N_2O was used as part of the anesthetic technique. The authors theorized that the volume of entrained air in children may be larger relative to their cardiac volume and may have contributed to the increased incidence of hypotension compared to the adult group. Although N_2O did not affect the incidence of hemodynamically significant VAE in our study, similar experimental data are unavailable in pediatric patients. The applicability of our findings to the pediatric population is unknown.

Pulmonary complications—more specifically, the appearance of new pulmonary infiltrates or pulmonary edema—after the occurrence of VAE have been described previously.[20-22] In each of the three patients in the current study with postoperative pulmonary complications that may have been related to VAE, the patient was extubated in the operating room but within the en-

suing 12 h experienced a relatively sudden onset of respiratory distress. Chest x-ray examination revealed a new pulmonary infiltrate or pulmonary edema in each patient (along with lobar collapse in one patient). It is difficult to attribute these complications directly to VAE, because other likely etiologies include aspiration due to lower cranial nerve dysfunction, mucous plugging in the bronchial tree, administration of naloxone, or some other unidentified factor. With only three patients experiencing pulmonary complications possibly related to VAE (two in the N_2O group and one in the no-N_2O group) of a total of 61 patients in the study who experienced VAE, there is no evidence to suggest that N_2O is a risk factor for this complication.

In the presence of a pneumocephalus, N_2O has been shown to increase cerebrospinal fluid pressure and intracranial pressure.[23,24] Because a pneumocephalus occurs to some degree in most patients who undergo a craniectomy in the sitting position, it has been suggested that when N_2O is used, its administration should be discontinued prior to dural closure to avoid the development of tension pneumocephalus.[10] However, other data suggest that intracranial pressure will not increase and tension pneumocephalus will not result when N_2O is being administered prior to dural closure and its administration is continued thereafter.[25] Presumably, under these circumstances, N_2O equilibrates with the intracranial air-containing cavity while the dura is open, such that after dural closure, no further volume expansion and/or significant intracranial pressure increase will occur. In our study, in patients in the N_2O group experiencing VAE who were undergoing craniectomy, N_2O administration was not reinstituted after completion of dural closure if it was not being administered during dural closure. In patients in whom N_2O was being administered before and during dural closure, its administration was continued after dural closure. This is consistent with our routine clinical practice and is based on the above considerations. Intracranial pressure was not monitored after dural closure in any patient undergoing a craniectomy in our study. It is, therefore, not possible to draw conclusions regarding the role of 50% N_2O and the development of tension pneumocephalus from data in our study. All that we can say is that in this series of 110 patients who underwent a craniectomy in the sitting position, the diagnosis of tension pneumocephalus was made in one patient in the no-N_2O group and in no patients in the N_2O-group.

Although our study was not designed to address the issue of paradoxical air embolism, another argument against the use of N_2O in patients at risk for VAE is that it will increase the size of an arterial air embolus and potentially exacerbate organ dysfunction on the basis of tissue ischemia.[26] Applicable data is not available from our study, and therefore we cannot draw any meaningful conclusions regarding this issue.

In conclusion, these data do not show an increase in the incidence or severity of VAE associated with the use of 50% N_2O to supplement an isoflurane–fentanyl-based anesthetic for sitting neurosurgical procedures if the administration of N_2O is discontinued immediately upon Doppler detection of VAE. In addition, when the anesthetic agents were administered so as to have the patient awake at the completion of surgery, we were unable to demonstrate any advantage related to the speed of emergence associated with the use of N_2O to supplement an isoflurane–fentanyl-based anesthetic. Our data do not provide a clear reason to use or to avoid the use of 50% N_2O during sitting neurosurgical procedures as it relates to the problem of VAE or the issue of emergence.

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