Nitrous Oxide Diffusion and the Second Gas Effect on Emergence from Anesthesia

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ABSTRACT

Background: Rapid elimination of nitrous oxide from the lungs at the end of inhalational anesthesia dilutes alveolar oxygen, producing "diffusion hypoxia." A similar dilutional effect on accompanying volatile anesthetic agent has not been evaluated and may impact the speed of emergence.

Methods: Twenty patients undergoing surgery were randomly assigned to receive an anesthetic maintenance gas mixture of sevoflurane adjusted to bispectral index, in air-oxygen (control group) *versus* a 2:1 mixture of nitrous oxide-oxygen (nitrous oxide group). After surgery, baseline arterial and tidal gas samples were taken. Patients were ventilated with oxygen, and arterial and tidal gas sampling was repeated at 2 and 5 min. Arterial sampling was repeated 30 min after surgery. Sevoflurane partial pressure was measured in blood by the double headspace equilibration technique and in tidal gas using a calibrated infrared gas analyzer. Time to eye opening and time extubation were recorded. The primary endpoint was the reduction in sevoflurane partial pressures in blood at 2 and 5 min.

Results: Relative to baseline, arterial sevoflurane partial pressure was 39% higher at 5 min in the control group ($P <$ 0.04) versus the nitrous oxide group. At 30 min the difference was not statistically significant. Time to eye opening (8.7 *vs.* 10.1 min) and time to extubation (11.0 *vs.* 13.2 min) were shorter in the nitrous oxide group *versus* the control group ($P <$ 0.04).

Conclusions: Elimination of nitrous oxide at the end of anesthesia produces a clinically significant acceleration in the

What We Already Know about This Topic

- The increase in the partial pressures of the other gases in the alveolar mixture resulting from the rapid uptake of high concentrations of nitrous oxide during inhalational anesthesia induction is known as the second gas effect.

What This Article Tells Us That Is New

- The second gas effect also occurs during emergence, with the rapid removal of nitrous oxide increasing the removal of other volatile anesthetics.

reduction of concentrations of the accompanying volatile agents, contributing to the speed of emergence observed after inhalational nitrous oxide anesthetic.

A NUMBER of studies[1–3] have shown that the rapid uptake of high concentrations of nitrous oxide at induction of inhalational anesthesia produces an increase in alveolar concentrations of oxygen and the accompanying volatile anesthetic agent. This process is known as the second gas effect. The effect is caused by the concentrating effect of nitrous oxide uptake on the partial pressures of the other gases in the alveolar mixture.[4] A more powerful effect on arterial volatile agent partial pressures has recently been demonstrated.[5]

During emergence from nitrous oxide anesthetic, rapid elimination of nitrous oxide from the lungs dilutes other alveolar gases, producing alveolar "diffusion hypoxia." This phenomenon is driven by the same mechanism as the second gas effect—but in the reverse direction. Fink's[6] original description of the syndrome predated demonstration of the second gas effect at induction by some years. The clinical problem it caused was readily managed by supplemental oxygen. In fact, Fink's work helped promote routine oxygen administration during recovery from anesthesia.[7] However, the relative importance of this dilutional effect on oxygenation was questioned by Rackow *et al.*,[8] among others,[9,10] who demonstrated that dilutional hypocapnia and consequent hypoventilation contributed to the clinical syndrome, along with airway obstruction, in the recovering patient.

A similar dilutional effect on the accompanying volatile anesthetic agent can be predicted on the same theoretical grounds as the effect on alveolar oxygen and carbon dioxide. An acute reduction in end-tidal halothane concentrations with sudden cessation of nitrous oxide was demonstrated by

Masuda *et al.*[11] The magnitude of the effect on blood partial pressures and its likely impact on the speed of emergence from inhalational anesthesia are undetermined. Therefore, we conducted a randomized controlled study to examine the effect of nitrous oxide elimination on the rate of decrease in sevoflurane concentrations in end-tidal gas and arterial blood at the end of inhalational anesthesia.

Materials and Methods

With approval by the Human Research Ethics Committee at the University of Melbourne at Austin Health (Australia), eligible patients were recruited to the study. Eligible patients were adults capable of giving informed consent who were undergoing general surgery that was anticipated to take at least 1 h and required general anesthesia where placement of an arterial blood pressure monitoring line for hemodynamic monitoring was considered appropriate by the attending anesthesiologist. Exclusion criteria included patients with a history of severe lung disease (defined as forced expiratory volume in 1 s less than 1.5 l or forced expiratory volume in 1 s/forced vital capacity less than 50%), symptomatic ischemic heart disease, super obesity (body mass index greater than 45), pregnancy, past history of severe postoperative nausea and vomiting, critically ill or immunocompromised patients, vitamin B12 or folate deficiency, or the presence of any gas-filled, space-occupying lesion.

Patients recruited were randomly assigned *via* sealed envelopes to receive an anesthetic maintenance gas mixture of either sevoflurane in air-oxygen (control group) or sevoflurane in a 2:1 mixture of nitrous oxide-oxygen (nitrous oxide group). After intravenous access and radial arterial catheter placement was achieved, premedication with 1–2 mg midazolam commenced. In addition, electrocardiographic monitoring, invasive blood pressure, oxygen saturation measured by pulse oximetry, tidal gas concentration monitoring, and bispectral index were established and the patient was preoxygenated. Anesthesia was induced with intravenous 1.5–2.5 mg/kg propofol, opioids (1–2 μg/kg fentanyl and/or morphine 0.05–0.1 mg/kg), and a neuromuscular blocker. The trachea was intubated and controlled ventilation was established (12–15 breaths/min) *via* a circle absorber breathing system. At this point, the study-allocated gas mixture commenced. Anesthesia was maintained with this mixture, with inspired sevoflurane concentration adjusted after the induction phase to achieve a bispectral index of 40–60. Nasopharyngeal temperature and expired tidal volume were monitored. Ventilation was adjusted to achieve an end-tidal carbon dioxide concentration of 28–33 mmHg. Normothermia was maintained using a forced-air warming device.

At the end of surgery, a baseline arterial blood sample (10 ml) was collected into a gas-tight 20-ml heparinized glass syringe sealed with a three-way stopcock, with an additional 1-ml sample for respiratory blood gas analysis. Tidal gas concentrations during 20 s were recorded simultaneously using a rapid gas analyzer (Capnomac Ultima; Datex-Ohmeda, Hel-

sinki, Finland) calibrated according to manufacturer instructions with proprietary calibration gas mixture. The device uses infrared absorption to measure carbon dioxide and anesthetic gases as well as a paramagnetic oxygen analyzer. Data were downloaded in real time as an analog signal to hard disk on a notebook computer (MacBook Pro; Apple Inc., Cupertino, CA) for subsequent measurement of baseline inspired partial pressure and end-tidal sevoflurane partial pressure (PA_0-S). Baseline hemodynamic (heart rate, blood pressure) and ventilatory (respiratory rate, expired tidal volume) data were recorded along with oxygen saturation measured by pulse oximetry, temperature, and bispectral index.

After data collection, neuromuscular blockade was reversed with intravenous 2.5 mg neostigmine and 0.4 mg glycopyrrolate. Fresh gas mixture changed to 100% oxygen at a flow rate of 9 l/min without alteration in ventilatory settings. After 2 min, an additional arterial blood gas sample was collected with simultaneous recording of tidal gas concentrations and other monitored data. Data collection was repeated at 5 min. The patient was loudly told to open his or her eyes. This command was repeated every 30 s. Time from command to eye opening was noted. Controlled ventilation was halted when the patient began to cough or strain. Extubation was performed after spontaneous respiration was established at a clinically adequate tidal volume and after oxygen saturation, as measured by pulse oximetry, reached at least 98%. Time to extubation was recorded. A final arterial blood gas sample was taken in the postanesthesia recovery unit at 30 min.

Arterial blood gas samples were processed in real time on the operating suite's blood gas analyzer (ABL 700 series; Radiometer, Copenhagen, Denmark). Arterial sevoflurane partial pressures at baseline (Pa_0-S) and at the other three specified time intervals (2 [Pa_2-S], 5 [Pa_5-S], and 30 [Pa_{30}-S] min) were measured from the 10-ml samples by a validated double headspace equilibration method as described previously.[12] Each sample was equilibrated in its glass syringe with an equal volume of air in an agitated warm water bath at body temperature for 1 h. Headspace gas was then decanted into a 10-ml glass syringe for analysis using the rapid gas analyzer (Radiometer). The process was repeated to allow calculation of partial pressure and partition coefficient for each patient. The gas analyzer was calibrated and its linearity in measurement of sevoflurane and nitrous oxide characterized by calibration against prepared standard gas mixtures as previously described.[12] Recorded tidal gas concentrations at each time point were analyzed to obtain end-tidal partial pressures at 2 (PA_2-S) and 5 min (PA_5-S).

The primary study endpoints were the differences between the control and nitrous oxide groups in the fraction of baseline partial pressure for sevoflurane remaining in arterial blood at 2 (Pa_2/Pa_0-S) and 5 min (Pa_5/Pa_0-S). A similar calculation was made for end-tidal concentrations at 2 (PA_2/PA_0-S) and 5 min (PA_5/PA_0-S), and for arterial and end-tidal carbon dioxide at each time point. Secondary endpoints were

Table 1. Patient Characteristics (N = 20)

| | Study Group | | |
Variables	Control	Nitrous Oxide	P Value
Age, yr	64.7 (18.4)	67.3 (13.0)	0.72
Sex, m/f	5/5	4/6	—
Weight, kg	72.5 (16.4)	79.1 (21.0)	0.44
Operative time, min	132.3 (43.0)	124.2 (62.6)	0.74
Minute ventilation, ml · min · kg	79.3 (17.8)	83.5 (16.8)	0.59
PIP, cm H_2O	18.1 (4.2)	19.1 (7.5)	0.73
SpO_2, %	98.9 (1.4)	97.2 (1.8)	0.02
Pa_0-S/barometric pressure, %	1.38 (0.40)	1.06 (0.36)	0.08
PA_0-S/barometric pressure, %	1.80 (0.30)	1.27 (0.34)	0.002
Pa_0CO_2, mmHg	43.5 (6.5)	41.3 (3.7)	0.40
PA_0CO_2, mmHg	31.4 (3.0)	31.3 (3.7)	0.97
Heart rate, beats/min	66.3 (10.5)	56.3 (5.9)	0.01
Mean arterial blood pressure, mmHg	79.6 (15.5)	71.1 (5.6)	0.12
Temperature, °C	35.8 (0.7)	35.6 (0.4)	0.31
Bispectral index	43.7 (8.5)	46.5 (8.6)	0.31

Pa_0CO_2 = baseline arterial carbon dioxide partial pressure; PA_0CO_2 = baseline end-tidal carbon dioxide partial pressure; Pa_0-S = baseline arterial sevoflurane partial pressure; PA_0-S = baseline end-tidal sevoflurane partial pressure; PIP = peak inspiratory pressure; SpO_2 = oxygen saturation measured by pulse oximetry.

comparisons between the two groups of bispectral index at 2, 5 and 10 min, time to eye opening, and time to extubation.

The null hypothesis tested was that elimination of nitrous oxide during emergence would not reduce measured PA/PA_0-S and Pa/Pa_0-S when compared with those in the control group.

Based on data collected during our previous study (N = 14),[5] which investigated the magnitude of the second gas effect on sevoflurane partial pressures after anesthesia induction, we expected that an effect of roughly similar magnitude would be present during elimination of nitrous oxide. However, given that baseline sevoflurane concentrations were unlikely to be similar in the two groups by the end of surgery, and allowing for a somewhat lower rate of nitrous oxide washout, we estimated that data from 20 patients would be required for analysis.

Comparisons were made using two-tailed t tests for unpaired data with the Bonferroni correction for multiple measurements in each patient (calculated raw P value was multiplied by the number of measurements made for each endpoint). In addition, two-way ANOVA was used to investigate whether any measured difference changed significantly over time. Best-fit curves for the primary endpoint were generated by the least-squares method using a power function of the form $f = at^b + c$, where t is time, a is amplitude, b is power, and c is offset. A two-tailed t test was used for all secondary endpoints after Kolmogorov-Smirnov normality testing. Statistical analyses were performed using Microsoft Office Excel 2008 (Microsoft Corp., Redmond, WA). Statistical significance was set at a P value of 0.05 or less.

Results

Twenty-one patients were recruited to the study. One patient in the nitrous oxide group was withdrawn from the study. This individual was a smoker undergoing nephrec-

tomy in the lateral position and developed acute hypoxemia from mucus plugging of the lower airways during repositioning at the end of the procedure and before completion of blood sampling, with arterial desaturation to 80%. Data from 10 patients in the nitrous oxide group (five former smokers and five nonsmokers) and 10 patients in the control group (four former smokers, two current smokers, and four nonsmokers) were collected for analysis. Demographic data and baseline measurements of relevant physiologic variables are listed in table 1.

In the control group, Pa/Pa_0-S at 5 min was 39% higher than in the nitrous oxide group ($P < 0.04$ using the t test with Bonferroni correction). There was a trend toward a similar difference at 2 min, but this result was not statistically significant ($P < 0.08$). The difference at 30 min (Pa_{30}/Pa_0-S) between groups was also not statistically significant on the t test. However, two-way ANOVA showed no evidence of group-time interaction ($P = 0.97$), suggesting that the difference between groups was maintained throughout the duration of the experiment.

Figure 1 shows Pa/Pa_0-S for both groups *versus* time (curve 1: control group; curve 2: nitrous oxide group) from baseline to 30 min after cessation of sevoflurane and nitrous oxide administration. Figure 2 displays absolute measured values for arterial sevoflurane for both groups, expressed as concentrations, with best-fit curves superimposed. Lying between the two curves for Pa/atmospheric pressure in the nitrous oxide and control groups in figure 2, this normalized curve indicates the specific contribution of the elimination of nitrous oxide to the difference in sevoflurane concentrations between the groups.

The difference between the control and nitrous oxide groups in PA/PA_0-S was smaller than that observed for arterial partial pressures (23.7% overall) and did not achieve
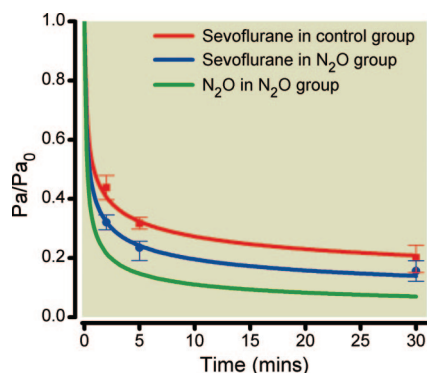
Fig. 1. Relative change in arterial sevoflurane and nitrous oxide partial pressures *versus* time. A comparison of arterial sevoflurane partial pressure (Pa) with baseline (Pa_0-S) is shown for both study groups *versus* time (curve 1: control group, curve 2: nitrous oxide group). Data represent measures from baseline to 30 min after cessation of sevoflurane and nitrous oxide administration. Error bars (1 standard error) at the 2, 5, and 30 min sampling points are shown with a line of best fit. A best fit line for measured nitrous oxide partial pressures in the nitrous oxide group is also shown for comparison with the volatile agent (curve 3).

statistical significance on the *t* test. Although end-tidal carbon dioxide concentrations fell by 10% in the nitrous oxide group at 2 and 5 min, in the control group, no significant change occurred ($P < 0.05$ between groups). Relative to baseline measurements, arterial carbon dioxide partial pressure declined significantly at 2 min in the nitrous oxide *versus* control group (-6.6 *vs.* -0.8%, $P = 0.05$ on the *t* test).
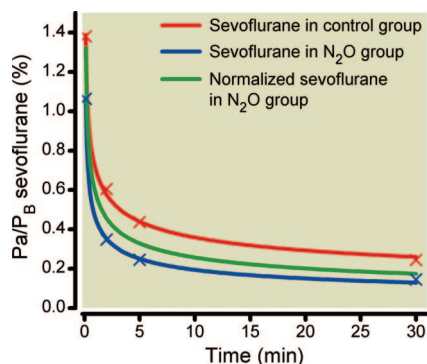

Fig. 2. Absolute change in arterial sevoflurane concentrations *versus* time. Absolute measured values for arterial sevoflurane partial pressure (Pa) for control and nitrous oxide groups are shown, expressed as percentage concentration ($P_B =$ atmospheric pressure). The lower baseline arterial sevoflurane concentration (1.06 *vs.* 1.38%) in the nitrous oxide *versus* control group is evident.

A normalized curve was created, derived from the best-fit curve for Pa/baseline (Pa_0-S) for the nitrous oxide group (fig. 1, curve 2). It was scaled to maintain its position relative to the control group curve *via* the following equation: (normalized nitrous oxide group Pa/P_B) = (nitrous oxide group Pa/Pa_0-S) $\times$ (control group Pa_0/P_B). This normalized curve indicates the specific contribution of dilution by nitrous oxide diffusion to the difference between the groups.

However, this difference was not statistically significant at 5 and 30 min (table 2).

There was no significant difference in bispectral index between groups at 2 or 5 min. Figure 3 shows the time to eye opening and the time to extubation for both groups. There was one outlier (more than 3 SDs from mean) in each group for both endpoints, both of which were excluded from analysis. Time to eye opening and time to extubation were significantly shorter ($P < 0.04$ for both endpoints on two-tailed *t* test) in the nitrous oxide group (mean [SD]): (8.7 [1.3] min and 10.1 [2.7] min) than the control group (11.0 [1.4] min and 13.2 [3.8] min).

Discussion

The current study demonstrates that early rapid diffusion or elimination of nitrous oxide at the end of inhalational anesthesia produces a significant acceleration in the reduction of partial pressure for accompanying volatile agent. During the first 5 min after cessation of anesthetic gas delivery, partial pressure of sevoflurane in arterial blood relative to baseline was 35% higher among patients for whom nitrous oxide was omitted, as compared with the patients who received nitrous oxide.

Although the trend we observed toward a more rapid reduction in end-tidal partial pressures of sevoflurane (PA/PA_0-S) in the nitrous oxide group was not statistically significant, it nevertheless parallels the findings of Masuda *et al.*[11] They demonstrated a smaller acute reduction in end-tidal halothane concentrations in patients 90 s after cessation of halothane where nitrous oxide was continued, compared with a subsequent measurement where both halothane and nitrous oxide were discontinued.[11] The clinical implications of this maneuver were unclear as it did not reflect normal clinical practice. In the current study, both study groups completed a standard clinical management protocol at cessation of inhalational anesthesia. The brief but significant decline in arterial carbon dioxide partial pressure observed in the nitrous oxide group is consistent with the findings of previous studies[8,9] that showed dilutional hypocapnia is part of the syndrome of "diffusion hypoxia." This difference did not persist into the recovery phase. Nitrous oxide elimination declines exponentially to relatively low rates after the first 5 min.[13] The accelerated excretion of other gases from the body might be expected to be transient, with only a brief change in blood and alveolar partial pressures.

Similarly, the difference in Pa/Pa_0-S between the groups in our study was not statistically significant at 30 min. However, a type 2 error in the final measurement is a possibility because examination of the best-fit curves in figure 1, and the absence of any group-time interaction on two-way ANOVA, suggests that the difference between treatment groups in Pa/Pa_0-S was maintained to some extent during recovery in the postanesthesia recovery unit. If this theory is true, the different behavior of carbon dioxide and volatile agent is probably the result of the continued metabolic production of carbon

Table 2. Primary and Secondary Endpoint Data for Partial Pressure Measurements of Sevoflurane and Carbon Dioxide

Endpoint	Group	Measurement Point					
		2 min	P Value	5 min	P Value	30 min	P Value
Pa/Pa_0-S	N_2O	0.32 (0.08)	—	0.23 (0.07)	0.04	0.16 (0.08)	—
	Control	0.44 (0.13)		0.32 (0.06)		0.20 (0.10)	
PA/PA_0-S	N_2O	0.18 (0.04)	—	0.14 (0.02)	—	NA	—
	Control	0.22 (0.07)		0.17 (0.06)			
Pa/Pa_0CO_2	N_2O	0.93 (0.03)	0.05	0.93 (0.04)	—	1.16 (0.14)	—
	Control	0.99 (0.05)		0.99 (0.10)		1.07 (0.08)	
PA/PA_0CO_2	N_2O	0.91 (0.02)	0.002	0.91 (0.06)	0.05	NA	—
	Control	0.99 (0.04)		0.97 (0.06)			

Data are expressed as mean (SD). Fraction of baseline sevoflurane partial pressure remaining in arterial blood (Pa/PAa_0-S) and end-tidal gas (PA/PA_0-S) by time point as well as baseline carbon dioxide partial pressure carbon dioxide in arterial blood (Pa/Pa_0CO_2) and end-tidal gas (PA/PA_0CO_2) for both study groups. P values for the t test adjusted for the Bonferroni correction are given only when statistically significant.
NA = not applicable.

dioxide, whereas the initial depletion of volatile agent in body tissues produced by early nitrous oxide diffusion is not compensated in the same way.

The effect of nitrous oxide diffusion was more powerful on the partial pressure of sevoflurane in arterial blood than in end-tidal gas. The former is more important because changes in blood partial pressure more directly reflect those occurring in the brain, and are therefore more likely to reflect changes in depth of anesthesia and speed of emergence. This difference between the effect on end-tidal and arterial partial pressures closely mirrors that shown in a recent study by our research group[5] that examined the magnitude of the second gas effect on induction of anesthesia and is explained by the same mechanism. Lung regions with moderately low ventilation/perfusion ratios contribute most powerfully to the uptake or elimination of soluble inert gases (*e.g.*, sevoflurane, nitrous oxide) and particularly to the concentrating and diluting effects of nitrous oxide. These lung units receive a large proportion of pulmonary blood flow and significantly contribute to the gas content of arterial blood. In contrast, end-tidal gas composition is heavily influenced by the contribution of high ventilation/perfusion lung units. These areas of the lung do not contribute as strongly to gas exchange. The

Fig. 3. Time to eye opening and time to extubation (s) for the control *versus* nitrous oxide study groups.

changes in end-tidal gas composition produced by the second gas effect are relatively diluted by alveolar dead-space gas from these lung units. This phenomenon has lead to an underestimation of the magnitude of the second gas effect during induction in previous studies[1–5,14–17] that measured only end-tidal gas concentrations, or that modeled lung gas exchange simplistically in a single homogeneous lung compartment. Rackow *et al.*[8] concluded that, during emergence from anesthesia, significant hypoxemia as a result of nitrous oxide diffusion was unlikely because mixed alveolar oxygen partial pressure was estimated to decrease by only 20% as a result of dilution. However, this explanation ignored the importance of regional heterogeneity of lung gas exchange on pulmonary capillary oxygenation. Other studies that have played down the clinical importance of diffusion hypoxia have focused on relatively healthy younger patients undergoing minor surgery, where ventilation/perfusion inhomogeneity is less severe.[18,19]

Arterial sevoflurane measurements in our control group compare closely with those made in a previous study by Katoh *et al.*,[20] who characterized the rate of decrease in volatile agent concentration at the end of anesthesia without nitrous oxide. At eye opening, mean sevoflurane concentration in arterial blood was 0.4% in that study,[20] compared with 0.35% (fig. 2) at the same point (11 min) in our study, which used an older patient sample. In our study, the shorter times to eye opening and to extubation in the nitrous oxide group parallel the findings of Jakobsson *et al.*[21] In that investigation, 42 patients underwent minor surgery during spontaneous ventilation *via* laryngeal mask breathing sevoflurane.[21] Time to removal of the laryngeal mask at the end of the procedure was 3.4 min shorter in the group that had received nitrous oxide.

A potential confounding factor in the current study was the lower heart rate and the trend toward lower blood pressure observed at baseline in the nitrous oxide group (table 1). This difference in hemodynamics between study groups would be
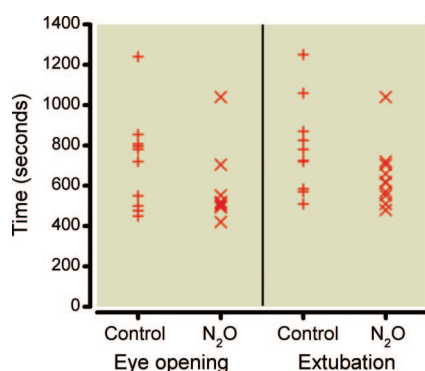
estimated to reflect a 10–20% lower cardiac output in the nitrous oxide group. The difference in heart rate was maintained at 2 min after cessation of anesthetic gas administration, but was not statistically significant at 5 min. During induction of inhalational anesthesia, a higher cardiac output slows the rise in end-tidal concentration relative to inspired (FA/FI).[22] A similar effect is expected on gas elimination and on the rate of reduction in Pa/Pa_0-S during emergence. This effect may have contributed to the observed difference between our two study groups. However, consideration of standard diagrams of the effect of cardiac output on FA/FI shows that a difference of 10–20% in cardiac output would produce a negligible effect.[13] To produce a difference in arterial sevoflurane partial pressures as large as we measured, the cardiac output in the control group would need to be approximately three times that in the nitrous oxide group—or an order of magnitude greater than the estimated difference in cardiac output in our study.[23,24]

Inclusion of nitrous oxide in the gas mixture reduces the inspired concentration and cumulative dose of volatile agent because of its "MAC (minimum alveolar concentration) sparing" effect. The magnitude of this effect in our study, as indicated by the baseline concentrations in the two groups, was a 22% reduction in arterial (fig. 2) and a 30% reduction in end-tidal sevoflurane concentrations. This reduction was less than that reported in earlier studies,[21,25] which found a sevoflurane MAC reduction of approximately 60%. The influence of bispectral index monitoring may explain this difference because the measure is unaffected by the presence of nitrous oxide.[26,27] Bispectral targeting may increase volatile agent use for this reason. The mean end-tidal sevoflurane concentration in the large ENIGMA trial,[28] where bispectral index monitoring was permitted as part of the protocol, was only 23% lower in the group randomized to receive nitrous oxide compared with their control group.

As well as the reduction in baseline volatile agent concentration it allows, previous studies[29–31] have suggested that inclusion of nitrous oxide may hasten awakening because of its different pharmacodynamic effects. Relative to their accepted MAC values, "MAC$_{awake}$" for nitrous oxide is nearly twice that for sevoflurane. The relative contribution of diffusion and MAC sparing effects on the reduction in volatile agent partial pressures by nitrous oxide can be estimated from our data and is shown in figure 2. The normalized curve for the nitrous oxide group in figure 2 is derived from the corresponding curve (curve 2) in figure 1, by scaling as described. It indicates the specific contribution of nitrous oxide diffusion to the difference between the groups in absolute arterial sevoflurane concentrations. It shows that more than half of the difference was the result of the dilutional effect it produced. This finding indicates that most of the reduction of volatile agent concentration observed where nitrous oxide is used was specifically the result of its diffusion (pharmacokinetic) effect in our study, with the remainder attributed to its direct MAC sparing (pharmacodynamic) effect.

Arguably, the diffusion or second gas effect during emergence is of more practical importance than the well-described second gas effect on anesthesia induction. An increase in alveolar and blood volatile agent partial pressure during induction can be achieved in the absence of nitrous oxide simply by "overpressure," exploiting the concentration effect by increasing the inspired concentration.[4] However, this result is not possible at the end of anesthesia because an inspired concentration of less than zero cannot be delivered.[13]

In summary, we found that elimination of nitrous oxide at the end of inhalational anesthesia produces a clinically significant acceleration in the reduction of concentrations of the accompanying volatile agents, an emergence-phase form of the second gas effect. This effect may be an important contributor to the speed of emergence observed after inhalational anesthesia with nitrous oxide.

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