

Magnitude of the Second Gas Effect on Arterial Sevoflurane Partial Pressure

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Background: A number of studies have demonstrated a faster rate of increase in end-expired partial pressure as a fraction of inspired (PA/Pi) for volatile agents in the presence of high concentrations of nitrous oxide, consistent with the second gas effect. However, no study has demonstrated a similar effect on arterial blood concentrations.

Methods: The authors compared arterial and end-tidal partial pressures of sevoflurane (Pa/Pi_{sevo} and PA/Pi_{sevo}) in 14 patients for 30 min after introduction of either 70% nitrous oxide or nitrous oxide-free gas mixtures to determine the magnitude of the second gas effect. Blood partial pressures were measured using a double headspace equilibration technique.

Results: Both Pa/Pi_{sevo} and PA/Pi_{sevo} were significantly higher in the nitrous oxide group than in the control group ($P < 0.001$ on two-way analysis of variance). This difference was significantly greater ($P < 0.05$) for Pa/Pi_{sevo} (23.6% higher in the nitrous oxide group at 2 min, declining to 12.5% at 30 min) than for PA/Pi_{sevo} (9.8% higher in the nitrous oxide group at 2 min) and was accompanied by a significantly lower Bispectral Index score at 5 min (40.7 vs. 25.4; $P = 0.004$).

Conclusion: Nitrous oxide uptake exerts a significant second gas effect on arterial sevoflurane partial pressures. This effect is two to three times more powerful than the effect on end-expired partial pressures. The authors explain how this is due to the influence of ventilation-perfusion scatter on the distribution of blood flow and gas uptake in the lung.

STUDIES by Severinghaus¹ and subsequent researchers²⁻⁴ have demonstrated that when the inspired concentration (Fi) of nitrous oxide is high, the early rate of uptake of nitrous oxide by the lungs is up to 1 l/min. Frumin *et al.*⁵ in 1961 postulated that this would substantially affect the concentration of other alveolar gases, and experimental data in dogs confirmed that arterial oxygen partial pressure (Pao₂) was elevated immediately after commencement of nitrous oxide.⁶

Epstein *et al.*⁷ in 1964 demonstrated a similar effect on the alveolar concentration (FA) of an accompanying volatile agent. In the first 10 min of nitrous oxide adminis-

tration, FA/Fi for halothane was higher when it was given in 70% nitrous oxide than in 10% nitrous oxide, and they called this the *second gas effect*. They attributed this to the further drawing in of inspired gas caused by the rapid uptake of nitrous oxide. Stoelting and Eger,⁸ in an experiment in dogs after prolonged halothane breathing, showed that FA/Fi for the volatile agent rose above 1.0 when nitrous oxide was introduced. This elegantly demonstrated that the effect was also due to an active concentrating effect on the second gas, within the alveolar compartment, caused by the uptake of nitrous oxide, and this finding has recently been confirmed in patients breathing the relatively insoluble anesthetic xenon in nitrous oxide.⁹

Other studies in humans have confirmed the existence of the second gas effect under clinical conditions, by demonstrating a faster rate of increase in FA/Fi for volatile agents in the presence of high concentrations of nitrous oxide.^{10,11} These studies have all used measured end-expired volatile agent concentrations to obtain FA. However, only one study has attempted to demonstrate the second gas effect on arterial blood concentrations.¹² Sun *et al.*¹² measured serial arterial blood concentrations of enflurane in 14 patients, and found no difference between patients breathing nitrous oxide or nitrous oxide-free gas mixtures. Their data led them to question the validity of the second gas effect as a clinical reality, and other authors have suggested that the effect is not clinically significant.¹³

We measured arterial and end-tidal partial pressures of sevoflurane in patients after induction of anesthesia to determine the existence and magnitude of the second gas effect.

Materials and Methods

With approval from the local institutional human research ethics committee, Austin Hospital, Melbourne, Australia, and with informed consent, 14 patients were recruited to the trial and randomly allocated to one of two groups. Eligible patients were adults with American Society of Anesthesiologists physical status I-III, undergoing general surgery, with a body mass index of less than 30 kg/m², and with no evidence of lung disease on the basis of history, examination, treatment or spirometry, where available. The control group (n = 7) was to receive general anesthesia with a fresh gas mixture of 2% sevoflurane in oxygen, and the nitrous oxide group (n = 7) was to receive 2% sevoflurane in 33% oxygen-67% nitrous oxide instead.

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Patients were sedated with 1.5–2.0 mg midazolam and peripheral intravenous and radial arterial cannulation performed. After preoxygenation, anesthesia was induced with propofol (1.5–2.0 mg/kg), an opioid and nondepolarizing neuromuscular blocker. The trachea was intubated, and volume-controlled ventilation was commenced by an Aestiva/5 anesthesia delivery system (Datex-Ohmeda, Helsinki, Finland) with its integrated compliance compensated ventilator, with tidal volumes of 7–10 ml/kg at a rate of 9–12 breaths/min, to achieve a stable end-tidal carbon dioxide partial pressure of 30–33 mmHg. All patients were initially ventilated with 100% oxygen and anesthesia maintained with intravenous propofol at a starting rate of $5.0 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, subsequently adjusted throughout the measurement period according to the Bispectral Index (BIS; Aspect Medical Systems, Norwood, MA) monitoring using a target BIS value of 40.

When stable hemodynamics and end-tidal carbon dioxide partial pressure had been achieved for 5 min, a baseline arterial blood gas sample was taken, after which the allocated fresh gas mixture was commenced at a fresh gas flow rate of 9 l/min to minimize wash-in time into the breathing system and keep the inspired partial pressure constant. Further 10-ml arterial blood samples were collected into heparinized glass syringes at 2, 5, 10, and 30 min after this point for the measurement of arterial sevoflurane partial pressure ($P_{a_{\text{sevo}}}$). Simultaneous recording of tidal gas concentrations sampled at the patient filter of the breathing system was made at each of these times to allow measurement of sevoflurane partial pressures in inspired ($P_{i_{\text{sevo}}}$) and end-expired ($P_{A_{\text{sevo}}}$) gas. Values from five consecutive breaths were taken and averaged for each measurement. Ventilatory and hemodynamic data from patient monitors and the blood gas analyzer (ABL 625; Radiometer, Copenhagen, Denmark) were recorded at each sampling time, as well as patient nasopharyngeal temperature and BIS score.

All measurements of sevoflurane in sampled gas were made by sidestream sampling by a single Capnomac Ultima gas analyzer (Datex-Ohmeda) calibrated according to the manufacturer's recommendations using a proprietary calibration gas cylinder. Analog data from the device was downloaded in real time *via* a 12-bit analog-digital converter card (USB 6009; National Instruments, Austin, TX) to a notebook computer (Powerbook G4; Apple Corp., Cupertino, CA) for storage, display, and analysis, which was performed using Labview 7.0 (National Instruments). This gives a resolution of 0.0025% (absolute) for sevoflurane concentration measurement.

The Capnomac uses paramagnetic measurement of oxygen, and near infrared absorption spectroscopy at different wavelengths to measure carbon dioxide, nitrous oxide, and the volatile anesthetic agents. The accuracy of the gas analyzer was previously characterized using a precise and reproducible primary volumetric

standard.¹⁴ This was performed across a wide range of sevoflurane concentrations, and repeated for sevoflurane in the presence of nitrous oxide, carbon dioxide, and water vapor. There was a tendency to underestimate the sevoflurane concentration with increasing concentrations of nitrous oxide, and a linear correction was incorporated for the measured nitrous oxide concentration in all raw sevoflurane measurements, as described previously.¹⁴ Otherwise, the device exhibited excellent accuracy and linearity.

Measurement of $P_{a_{\text{sevo}}}$ in each arterial blood sample was performed using a double "headspace" equilibration method. Our technique has been validated by comparison with tonometered blood samples,¹⁴ with agreement comparable to that achieved by previous workers using gas chromatography.^{15,16} The blood was immediately transferred into a 20-ml glass syringe with a three-way stopcock attached, into which a further 10 ml of air was then drawn up as the headspace for equilibration, retaining any bubbles created during the sampling of the blood. The syringes were then placed into an agitated warm water bath set to the patient's body temperature for the first equilibration.

After a minimum of 1 h,¹⁷ the contents of the gas headspace in each 20-ml syringe were transferred *via* the three-way stopcock to a 10-ml glass syringe (to prevent the possibility of inadvertent suction of blood into the analyzer if the headspace gas was delivered directly from the 20-ml equilibration syringe). The sidestream gas sampling line of the analyzer was attached to this *via* the stopcock, the contents of the 10-ml syringe were delivered to the analyzer (and the stopcock was then opened to atmosphere to eliminate any pressure artifact during sampling), and its measurements were downloaded to the computer as described above. This produced a stable concentration plateau from which gas concentrations could be precisely read. After any remaining headspace gas was expelled from the 20-ml syringe, a further 10 ml of air was drawn up into it, and the process described was repeated for the second equilibration. At each stage, appropriate corrections were made for dilution of headspace gas by air in the volume of the stopcocks during transfer.

The partial pressure of the volatile agent in the blood sample before the equilibration process was then calculated as previously described.¹⁴ The two sequential headspace equilibrations effectively allow calculation of both the original partial pressure ($P_{a_{\text{sevo}}}$) of the agent in the blood sample and its blood/gas partition coefficient, from mass balance principles. Our technique is based on similar mass balance principles to the multiple headspace equilibration methods described by previous authors,^{15–17} with the exception that we used the change in the calculated partial pressure change of insoluble balance gas (atmospheric nitrogen) in the headspace to determine the relative volumes of the headspace gas in

the syringe after each equilibration. Nitrogen partial pressure was calculated by subtraction of the sum of all the other gas partial pressures (ΣP_{gases}), as well as water vapor pressure, from atmospheric (P_B). Thus,

$$P_{a_{sevo}} = P_{1_{sevo}} \cdot \left[\frac{P_B - \sum P_{1_{gases}} - P_{1_{H_2O}}}{P_B - \sum P_{2_{gases}} - P_{2_{H_2O}}} \cdot \left(\frac{P_{1_{sevo}}}{P_{2_{sevo}}} - 1 \right) + 1 \right],$$

where $P_{1_{sevo}}$ and $P_{2_{sevo}}$ are the measured partial pressure of sevoflurane after the first and second equilibrations, and $\Sigma P_{1_{gases}}$ and $\Sigma P_{2_{gases}}$ are the sums of the partial pressures of all the gases measured by the gas analyzer after each equilibration. In each case, saturated water vapor pressure (P_{H_2O}) is known at the measured temperature. Significant volume changes can occur in the headspace gas during equilibration, especially when high concentrations of nitrous oxide are present in the blood sample. This approach has been shown to reliably deal with this,¹⁴ avoiding potential errors in headspace volume measurement.

The ratio of P_A and P_a for sevoflurane to its inspired partial pressure P_I was then calculated ($P_A/P_{I_{sevo}}$ and $P_a/P_{I_{sevo}}$) for each sampling time.

Statistical Analysis

Comparison of $P_A/P_{I_{sevo}}$ between the control and nitrous oxide groups was made at each sampling time interval and overall, using an unpaired *t* test. The same was done for $P_a/P_{I_{sevo}}$. In addition, the mean difference overall between the two groups in $P_A/P_{I_{sevo}}$ was compared with that for $P_a/P_{I_{sevo}}$ using a paired *t* test. A significance threshold of $P < 0.05$ was used, which was adjusted at each of the four sampling time points using a Bonferroni correction for multiple comparisons. Comparison between the two groups over the measurement period in both $P_A/P_{I_{sevo}}$ and $P_a/P_{I_{sevo}}$ was also conducted using two-way analysis of variance, which was also examined for the presence of a group-time interaction.

Results

There were four female and three male patients recruited to each group. There were three ex-smokers and one current smoker in the control group and two ex-smokers in the nitrous oxide group. Comparison of demographic and other characteristics between the two groups is listed in tables 1 and 2. Average (SD) values from all patients for baseline P_{aO_2} , P_{aCO_2} , and hemoglobin are given in table 1. Table 2 gives values for variables (ventilatory and hemodynamic variables, temperature, and BIS) that were measured over the four sampling times. There was a higher end-tidal carbon dioxide partial pressure in the nitrous oxide group at the 5-, 10-, and 30-min points, suggesting that this group was relatively

Table 1. Baseline Patient Data

Variable	Control Group	N ₂ O Group	P Value
Age, yr	64.3 (17.2)	63.3 (10.5)	0.9
Height, cm	163 (14)	166 (11)	0.66
Weight, kg	80.8 (18.6)	78.3 (6.5)	0.76
P _{aO₂} , mmHg	433 (112)	393 (104)	0.5
P _{aCO₂} , mmHg	38.8 (3.9)	38.2 (3.8)	0.76
Hb, g/dl	11.9 (2.0)	14.2 (2.4)	0.08

Comparison of baseline demographic and blood gas data between the two groups, using an unpaired *t* test. Values are mean (SD).

Hb = hemoglobin concentration; N₂O = nitrous oxide; P_{aCO₂} = arterial carbon dioxide partial pressure; P_{aO₂} = arterial oxygen partial pressure.

underventilated compared with the control group, although the associated difference in measured minute ventilation was not statistically significant. There was also a significant difference in BIS score (40.7 in the control group vs. 25.4 in the nitrous oxide group; $P = 0.004$) at the 5-min measurement point.

Figure 1 shows $P_A/P_{I_{sevo}}$ and $P_a/P_{I_{sevo}}$ for both the control and nitrous oxide groups. Fitted curves are added to indicate rate of increase in each variable from zero. Where nitrous oxide was present, $P_A/P_{I_{sevo}}$ was significantly higher than in the control group at 2 min (9.8% higher; $P = 0.011$) and 5 min ($P = 0.003$), but this difference declined

Table 2. Patient Data at Each Measurement Point

Variable	Time, min	Control Group	N ₂ O Group	P Value
PE'co ₂ , mmHg	2	30.0 (1.6)	31.1 (4.3)	0.26
	5	29.5 (1.9)	32.2 (3.4)	0.03
	10	29.6 (1.9)	32.7 (2.9)	0.008
	30	29.8 (2.1)	33.5 (2.9)	0.003
MV, l/min	2	6.2 (1.8)	5.8 (1.3)	0.55
	5	6.1 (1.3)	5.5 (1.2)	0.39
	10	6.2 (1.2)	5.5 (1.2)	0.26
	30	6.2 (1.4)	5.5 (1.1)	0.94
PIP, cm H ₂ O	2	20.4 (2.9)	19.4 (1.5)	0.43
	5	19.9 (2.9)	17.7 (1.5)	0.11
	10	19.9 (2.7)	18.3 (2.1)	0.24
	30	21.0 (3.4)	18.6 (2.2)	0.14
MAP, mmHg	2	85.0 (16.1)	90.9 (11.3)	0.45
	5	78.3 (12.5)	77.7 (17.6)	0.94
	10	77.7 (16.0)	82.6 (11.0)	0.52
	30	92.9 (16.3)	85.7 (10.2)	0.34
HR, beats/min	2	69.9 (13.5)	70.3 (10.2)	0.95
	5	67.3 (13.8)	64.7 (11.5)	0.71
	10	68.7 (18.6)	60.1 (10.8)	0.31
	30	76.7 (16.9)	61.7 (13.2)	0.10
Temp, °C	2	36.0 (0.5)	35.7 (0.5)	0.20
	5	35.9 (0.5)	35.6 (0.5)	0.23
	10	35.9 (0.5)	35.5 (0.5)	0.15
	30	35.9 (0.4)	35.4 (0.3)	0.053
Bispectral Index	2	50.1 (12.2)	38.6 (16.0)	0.15
	5	40.7 (6.6)	25.3 (8.5)	0.004
	10	42.1 (8.5)	33.9 (11.5)	0.15
	30	35.0 (17.6)	35.6 (6.9)	0.94

Comparison of ventilatory, hemodynamic, temperature, and Bispectral Index data between the two groups, using an unpaired *t* test. Values are mean (SD).

HR = heart rate; MAP = mean arterial pressure; MV = minute ventilation; N₂O = nitrous oxide; PE'co₂ = end-tidal carbon dioxide partial pressure; PIP = peak inspiratory pressure; Temp = nasopharyngeal temperature.

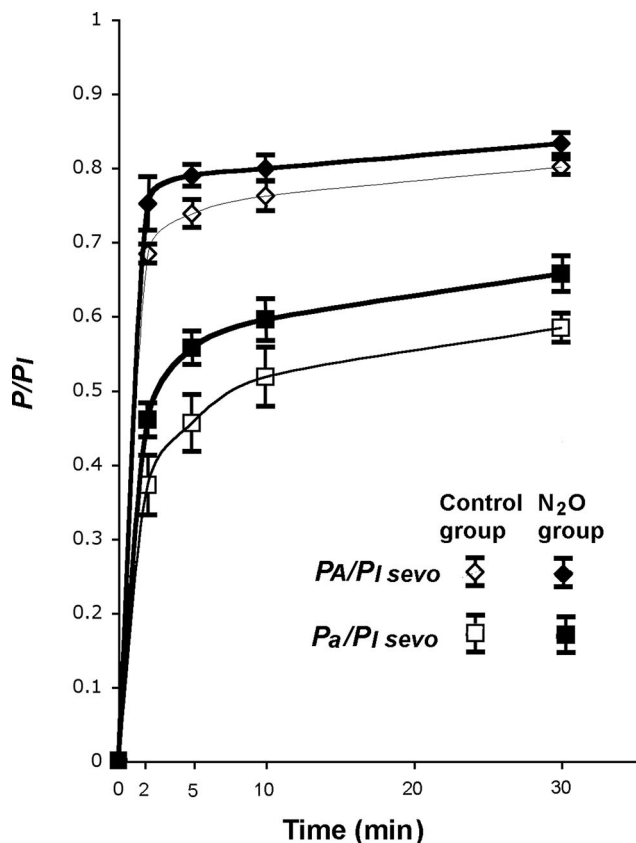


Fig. 1. The partial pressures of sevoflurane (as a fraction of inspired partial pressure) in end-expired gas ($P_A/P_{i\text{sevo}}$; diamonds) and arterial blood ($P_a/P_{i\text{sevo}}$; squares). Fitted curves are added to indicate rate of increase in each variable from zero. Heavy lines = nitrous oxide (N_2O) group; thin lines = control (no N_2O) group. Error bars (± 1 SE) are shown for each sampling time point.

and at 10 and 30 min did not reach statistical significance using a *t* test adjusted for multiple comparisons.

The effect of nitrous oxide on $P_a/P_{i\text{sevo}}$ was considerably more powerful, however. At 2 min, it was 23.6% higher in the nitrous oxide group, this difference declining to 12.5% at 30 min ($P < 0.01$ at 2, 5, and 30 min).

Across the measurement period overall, both $P_A/P_{i\text{sevo}}$ and $P_a/P_{i\text{sevo}}$ were higher in the nitrous oxide group ($P < 0.001$). This overall difference was significantly greater for $P_a/P_{i\text{sevo}}$ than for $P_A/P_{i\text{sevo}}$ ($P < 0.05$).

Two-way analysis of variance confirmed a statistically significant difference between the control and nitrous oxide groups in both $P_A/P_{i\text{sevo}}$ and $P_a/P_{i\text{sevo}}$ over the period of measurement ($P < 0.001$ for each variable). This found no evidence of a group-time interaction for either $P_A/P_{i\text{sevo}}$ ($P = 0.63$) or $P_a/P_{i\text{sevo}}$ ($P = 0.93$), confirming that the difference between control and nitrous oxide groups in both $P_A/P_{i\text{sevo}}$ and $P_a/P_{i\text{sevo}}$ was consistent across the measurement period.

Discussion

Several studies, in animals and humans, have demonstrated a higher rate of increase of P_A/P_i for a volatile

agent where a high concentration of nitrous oxide is administered,⁸⁻¹¹ confirming the existence of the second gas effect, as originally demonstrated more than 40 yr ago.⁷ Our results are consistent with this. The magnitude of the effect of nitrous oxide uptake on $P_A/P_{i\text{sevo}}$ we found was similar to that recently demonstrated by Hendrickx *et al.*¹¹ and similar also to the effect on P_A/P_i for desflurane shown by Taheri and Eger.⁹ However, the second gas effect we found on arterial sevoflurane partial pressure was much more substantial, and this has not previously been shown.

Most previous studies in this area have used gas chromatography to measure the partial pressure of volatile agent. Our technique used a clinical infrared gas analyzer to measure sevoflurane in both tidal gas and blood samples, which allowed processing of all samples on site immediately after collection. Because of the concern that overlap of infrared absorption spectra of these gases or related phenomena, such as collision broadening, might impair its accuracy,¹⁸ it was necessary for us to carefully calibrate the device, using a precise and reproducible volumetric standard, as described previously.¹⁴ We then validated our double headspace equilibration technique for measurement of volatile agent partial pressures in blood against tonometered blood, and demonstrated accuracy comparable to that achieved by previous studies using gas chromatography,¹⁵⁻¹⁷ in both the presence and the absence of nitrous oxide. This confirms the reliability of our results in the current study. It should be noted that $P_a/P_{i\text{sevo}}$ was virtually unaltered by the correction required for the presence of nitrous oxide, which was applied to raw sevoflurane measurements from the analyzer. This was because P_a/P_i for nitrous oxide was close to 1.0. The same correction imposed on $P_a/P_{i\text{sevo}}$ was also negligible, for similar reasons.

The traditional explanation of the second gas effect⁸ used a simplified model designed to show how large-volume uptake of nitrous oxide within a lung compartment concentrates the other alveolar gases. This is reproduced in part in figure 2. This traditional model depicts an inspired nitrous oxide concentration of 80%, with 19% oxygen and 1% "second gas," and uptake by blood of 50% of the inspired volume of nitrous oxide as a single step. The resulting increase in the concentration of the oxygen and second gas due to the concentrating effect is shown to the right. The second gas has been concentrated to 1.7%. For simplicity, the model only considers uptake of the nitrous oxide and not of the other gases. For the purposes of the current study, this is treated in figure 2 as a "constant inflow" model,¹⁹ in which we ignore the further step of indrawing of further inspired gas to replace the lost volume (this in fact does not alter the final alveolar equilibrium concentrations achieved¹⁹). The concentrations in blood leaving the lung have been added at the bottom of the diagram.

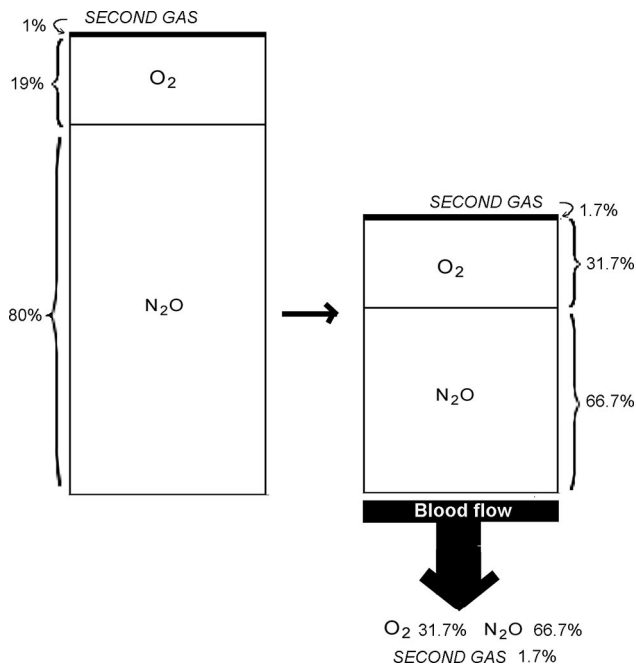


Fig. 2. The traditional diagram depicting the mechanism for the second gas effect in a simplified model of the lung with an inspired nitrous oxide (N_2O) concentration of 80%, 19% oxygen (O_2), and 1% “second gas” (left). The increase in the concentration of the oxygen and second gas is shown to the right, where half of the inspired volume of nitrous oxide is taken up by blood (heavy lines at bottom). The concentrations of the gases in blood leaving the lung are shown at the bottom.

In reality, the rate of uptake of nitrous oxide by pulmonary blood is not as great as the 50% depicted in the traditional diagram, partly because of rapidly increasing mixed venous nitrous oxide partial pressure. In addition, the high rate of uptake in the first few minutes of nitrous oxide breathing is largely due to wash-in of nitrous oxide into the patient’s functional residual capacity, rather than true alveolar–capillary gas uptake.^{20,21} This has led some commentators to question the significance or even the reality of the second gas effect.^{12,13} The only previous study to compare arterial blood concentrations of volatile agent between control and nitrous oxide groups was conducted by Sun *et al.*¹² in patients breathing a low inspired concentration (0.2%) of enflurane. They were unable to find any difference between their groups in enflurane concentrations in blood over the first 5 min and concluded that “the second gas effect is not a valid concept.” However, their finding was not surprising, given that, in their subjects, they were unable to show any second gas effect on end-expired volatile agent concentrations either. Their failure to do so contradicts all other published studies in this area.^{8–11}

The second gas effect we found on arterial sevoflurane partial pressures was substantial. $P_a/P_{i_{sevo}}$ increased more than 20% faster in the nitrous oxide group for the first 5 min after induction. An effect of this magnitude possibly has significant clinical implications. At a given inspired concentration of volatile agent, the rate of in-

duction of anesthesia may be expected to be significantly faster with nitrous oxide, not only because of the additional anesthetic effect of nitrous oxide itself, but because of a much faster rate of increase of arterial volatile agent partial pressure as well. Our finding of a significantly lower BIS score in the nitrous oxide group at 5 min is therefore of interest. It has been shown that nitrous oxide produces little or no independent depression of BIS,^{22,23} which suggests that the difference we observed was due to the higher early arterial sevoflurane partial pressures achieved in the nitrous oxide group. From these data, it seems that a measurable effect on depth of anesthesia accompanies the second gas effect on arterial volatile agent partial pressure.

Our data suggest that in the other previous studies in this field, the focus on end-expired volatile agent concentrations has overlooked the real magnitude and significance of the second gas effect. Although end-expired anesthetic gas concentrations are more easily and non-invasively measured, it is arterial partial pressures that are more clinically important, because they most directly determine the depth of anesthesia. The second gas effect on arterial partial pressures we found was two to three times more powerful than that measured on end-expired partial pressures.

The reasons for this lie in the effect of ventilation–perfusion scatter on the distribution of gas uptake in the lung. This is not revealed by the simple one-compartment model in figure 2. Ventilation–perfusion inhomogeneity increases in patients during anesthesia and with increasing age.^{24–27} In figure 3, the hypothetical lung of figure 2 is divided into two compartments, in which the blood flow is unevenly distributed so that the left hand compartment now receives three fourths of the blood flow. As before, 50% of the nitrous oxide is taken up in total, but this uptake is distributed between the compartments in proportion to their blood flow. The resulting concentrations of the alveolar gases in each compartment are shown, as well as the flow-weighted final concentrations in blood leaving the lung. The concentration of the second gas in arterial blood is now 2.2%. The inhomogeneous lung has produced a more powerful second gas effect on arterial concentrations. This will not be reflected in the volume-weighted concentration of second gas in combined expired alveolar gas from the two compartments.

Figures 2 and 3 represent the component of the second gas effect that has been referred to as the “concentrating effect,”⁸ which Korman and Mapleson¹⁹ referred to as a “constant inflow” model, and does not include further uptake of inspired gas to replace the lost volume (“constant outflow”). Their more complete adaptation of the original simplified diagram depicted in figure 2 showed that the final equilibrium concentrations achieved are the same as those calculated by the constant inflow model (although the volumes taken up are

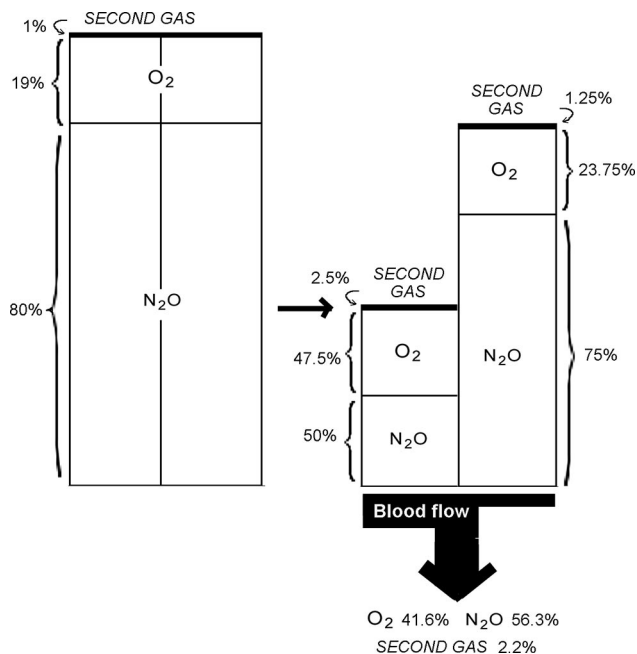


Fig. 3. Modified version of figure 2 in which the hypothetical lung is divided into two compartments, so that the left-hand compartment now receives three fourths of the blood flow. Uptake of nitrous oxide (N₂O) in the compartments is kept proportional to their blood flow. The resulting concentrations of the alveolar gases in each compartment are shown, as well as the flow-weighted concentrations in blood leaving the lung. Inhomogeneity of blood flow has exaggerated the second gas effect, in comparison with figure 2. O₂ = oxygen.

different), so the mechanism depicted in figure 3, although simplified, is useful in conveying the basis for our findings. The presence of a higher end-tidal carbon dioxide partial pressure in the nitrous oxide group in our study suggests that the nitrous oxide group was relatively under-ventilated compared with the control group. This presumably occurred because of the lower expired minute ventilation associated with the uptake of nitrous oxide in this group, consistent with a “constant inflow” model.

This difference between the second gas effect on blood and expired gas concentrations is because the uptake of nitrous oxide is perfusion driven and confined mainly to those lung compartments with a lower ventilation-perfusion ratio. These compartments receive most of the blood flow and predominantly determine the composition of gases in arterial blood. Most of the nitrous oxide uptake occurs in moderately low ventilation-perfusion ratio lung units, in which the rate of nitrous oxide uptake is large relative to their alveolar ventilation. In addition, the simple two-compartment model described in figure 3 ignores inhomogeneity of ventilation of the compartments, which would further accentuate the difference between the second gas effect on arterial blood and end-tidal gas concentrations.

The influence of ventilation-perfusion inhomogeneity also explains how a relatively low total rate of nitrous oxide uptake still produces a significant second gas effects. The concentrating effects produced are powerful

enough to remain substantial, even after total nitrous oxide uptake rates decline to low levels, as occurs during maintenance phase anesthesia.¹⁻⁴ Hendrickx *et al.*¹¹ showed a persistent second gas effect on end-tidal sevoflurane concentrations in anesthetized patients and suggested that this was driven by ventilation-perfusion scatter. Their conclusions were prompted by the findings of lung modeling by us using physiologic distributions of ventilation and perfusion, which predicted a persisting second gas effect on PaO₂.²⁸ This has been confirmed in patients^{29,30} and was similar in magnitude to the 12% increase in Pa/Pi_{sevo} we found at 30 min in the current study.

In summary, we have shown that in patients breathing sevoflurane in 70% nitrous oxide, the second gas effect on arterial volatile agent partial pressures was considerably more powerful than the accompanying effect on end-tidal concentrations, and that this difference arises from the effect of ventilation-perfusion scatter on gas exchange during inhalational anesthesia.

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