Second gas effect of N₂O on oxygen uptake

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Purpose: The concept of the second gas effect is well known, however, there have been no studies that showed the relationship between alveolar oxygen concentration and arterial oxygen tension (PaO₂) after the inhalation of nitrous oxide (N₂O) in humans. The purpose of this study was to examine the changes in both end-tidal oxygen fraction (F_{ET}O₂) and PaO₂ after N₂O inhalation in patients under general anesthesia.

Methods: Fifteen patients scheduled for elective orthopedic surgery were enrolled in this study. Anesthesia was maintained with the continuous infusion of propofol and with nitrogen (N₂) and oxygen (O₂) (6 L·min⁻¹, F_IO₂, 0.33). In all patients, the lungs were ventilated with a Servo 900C ventilator equipped with a gas mixer for O₂, N₂O, and N₂. After obtaining baseline data, N₂ was replaced with N₂O maintaining F_IO₂ constant at 0.33. The changes in fractional concentration of O₂, N₂O, and N₂ were continuously measured using mass spectrometer in a breath-by-breath basis. PaO₂ and hemodynamic data were obtained at 1, 5, 10, 30 and 60 min after the start of N₂O inhalation.

Results: Five minutes after N₂O inhalation, F_{ET}O₂ increased from 0.27 ± 0.01 to 0.31 ± 0.02 (*P* < 0.01) and PaO₂ increased from 172.0 ± 22.5 mmHg to 201.0 ± 10.3 mmHg (*P* < 0.01). These effects produced by N₂O were observed for 30 min.

Conclusions: These results confirm the concept of second gas effect of N₂O on oxygen uptake in humans and provide evidence that the PaO₂ increase correlated with the increase in F_{ET}O₂ after N₂O inhalation.

Objectif : Le concept de l'effet du deuxième gaz est bien connu, mais aucune étude n'a montré la relation qui existe entre la concentration alvéolaire d'oxygène et la pression artérielle d'oxygène (PaO₂) à la suite d'inhalation de protoxyde d'azote (N₂O) chez l'humain. L'objectif de la présente étude était d'examiner les changements de la fraction d'oxygène de fin d'expiration (F_{ET}O₂) et de PaO₂ après l'inhalation de N₂O chez des patients sous anesthésie générale.

Méthode : Admis pour une intervention orthopédique planifiée, 15 patients ont participé à l'étude. L'anesthésie a été maintenue avec une perfusion continue de propofol et un mélange azote-oxygène (6 L·min⁻¹, F_IO₂, 0,33). La ventilation pulmonaire a été assurée par un ventilateur Servo 900C muni d'un mélangeur de gaz pour O₂, N₂O, et N₂. Après l'obtention des données de base, N₂ a été remplacé par N₂O, maintenant ainsi la F_IO₂ constante à 0,33. Les changements de concentration fractionnaire de O₂, N₂O, et de N₂ ont été mesurés continuellement, pour chaque respiration, en utilisant un spectromètre de masse. On a noté la PaO₂ et les paramètres hémodynamiques à 1, 5, 10, 30 et 60 min après le début de l'inhalation de N₂O.

Résultats : Cinq minutes après l'inhalation de N₂O, la F_{ET}O₂ a augmenté de 0,27 ± 0,01 à 0,31 ± 0,02 (*P* < 0,01) et la PaO₂ s'est élevée de 172,0 ± 22,5 mmHg à 201,0 ± 10,3 mmHg (*P* < 0,01). Ces effets produits par le N₂O ont été observés pendant 30 min.

Conclusion : Les résultats confirment le concept de l'effet du deuxième gaz lié au N₂O sur le captage d'oxygène chez l'humain et ils prouvent que l'augmentation de la PaO₂ est en corrélation avec l'élévation de la F_{ET}O₂ après l'inhalation de N₂O.

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THE concentration¹ and second gas effects² were first demonstrated in dogs. Increasing the inspired concentration of N₂O concentrated both N₂O and any gas delivered concurrently (the second gas) due to a difference of the blood/gas partition coefficient between N₂ and N₂O. Thus, rapid and massive initial uptake of N₂O during the induction of anesthesia increased the delivery of both gases to the lung. Since then, many studies have confirmed the existence of the second gas effect for halothane^{3,4} and for oxygen⁵ in human and for carbon dioxide (CO₂) in cats.⁶ Two theoretical studies^{7,8} supported and improved the concept of second gas effect. However, recent reports have questioned the applicability of above mentioned explanations to clinical practice. Sun *et al.*⁹ showed that N₂O did not affect the alveolar and blood concentration of the second gas (enflurane) under controlled constant volume ventilation. In addition, Lin *et al.*¹⁰ pointed out the importance of taking functional residual capacity (FRC) into consideration in calculating the gas uptake through the alveolar membrane. Thus, there is still controversy regarding its interpretation of the second gas effect and sufficient reason to re-examine the effect on oxygen in humans. No studies have shown the relationship between alveolar oxygen concentration and PaO₂ after N₂O inhalation.

In previous papers, the end-tidal and inspired gas samples were intermittently collected for concentration analysis. Thus, the ratio of alveolar (end-tidal) concentration (F_A) to the inspired concentration (F_I) was used to present data. In this study, we used the respiratory gas mass spectrometer (RGMS) that allowed us to measure continuously fractional concentrations of both inspiratory and expiratory gases in patients under general anesthesia on a breath-by-breath basis. This study was undertaken to test the concept that the second gas effect of N₂O on oxygen exists in humans and to clarify the relationship between alveolar oxygen concentration and PaO₂ after N₂O inhalation using RGMS.

Methods

After obtaining approval from the institutional Ethical Committee for Human Research and written informed consent, 15 patients classified as ASA physical status I or II (Table I), scheduled for minor orthopedic surgery of the lower extremities were enrolled in this study. Patients with clinically important pulmonary, cardiovascular, hepatic, renal, or neurological diseases were excluded. Also excluded were patients who were taking medications known to influence anesthetic requirements.

No premedication was given on the ward. After arrival in the operating room after having fasted for at least eight hours, routine monitors were applied and lactated Ringer's solution was administered. After three minutes preoxygenation, anesthesia was induced with 2 mg·kg⁻¹ propofol and the trachea was intubated after administration of 0.1 mg·kg⁻¹ vecuronium. Lidocaine, 0.5 mg·kg⁻¹, was used to minimize pain on injection with propofol. Anesthesia was maintained with the continuous infusion of 100-120 µg·kg⁻¹·min⁻¹ propofol and with inspired gas mixtures, 6 L·min⁻¹: N₂ and O₂ (F_IO₂, 0.33). A radial artery catheter was inserted to monitor systemic blood pressure and for blood sampling. During surgery, 0.05 mg·kg⁻¹·hr⁻¹ vecuronium, was continuously infused. A small dose of fentanyl, 0.05 mg, or ephedrine, 2 mg, was administered to maintain heart rate and systemic blood pressure within ± 20 % of initial recordings. In all patients, the lungs were ventilated with Servo 900C ventilator (Siemens-Elema, Sweden) in a volume-controlled mode. This ventilator was equipped with a gas mixer to change inspired gas concentration quickly. Ventilatory settings were tidal volume (V_T) = 10-14 ml·kg⁻¹ (adjusted to maintain P_{ET}CO₂ between 35-40 mmHg with patients in the supine position), ventilator frequency (f) = 12/min, and positive end-expiratory pressure (PEEP) = 3 mmHg. These settings were not changed throughout the study period. Body temperature was monitored and maintained at 36-37°C.

Respiratory gas concentrations were continuously measured using the respiratory gas mass spectrometry (AMIS 2000SP, Innovision A/S, Odense, Denmark) sampling gases from the slip-joint port of the endotracheal tube. Respiratory gas was sampled through a 0.2-mm-ID Teflon tube at a rate of 15 ml·min⁻¹ and respiratory data were saved on a PC personal computer. The response time of this respiratory analyzer is 60 msec. This system allowed us to measure the respiratory gas concentration on a breath-by-breath basis. Proper calibration of the mass spectrometer was verified using calibration gases dictated by the manufacturer's instructions. After baseline data were obtained, inspiratory N₂ was replaced with N₂O by switching the gas mixer dial quickly from air/oxygen mode to

TABLE I Demographic data

Number of patients	15
Sex (male/female)	8/7
Age (yr)	47.1 ± 8.7
Weight (kg)	59.6 ± 5.4
ASA (1/2)	14/1
Duration of surgery (min)	135 ± 24
Duration of anesthesia (min)	187 ± 31

TABLE II Changes in hemodynamic data of blood gas analysis and body temperature

	Baseline	1	5	10	15	30	60 (min)
HR (beats·min ⁻¹)	75.3 ± 5.5	72.7 ± 6.5	72.3 ± 4.5	72.9 ± 4.2	74.5 ± 6.7	75.6 ± 7.6	76.7 ± 5.4
SBP (mmHg)	112.6 ± 15.1	108.8 ± 10.6	109.1 ± 9.7	110.5 ± 10.9	113.7 ± 12.5	113.5 ± 12.6	115.9 ± 14.6
pH	7.45 ± 0.03	7.44 ± 0.04	7.44 ± 0.04	7.44 ± 0.03	7.44 ± 0.04	7.43 ± 0.05	7.43 ± 0.03
PaCO ₂ (mmHg)	35.4 ± 3.8	36.8 ± 3.8	36.3 ± 4.1	36.7 ± 3.4	36.6 ± 4.6	36.4 ± 5.2	36.6 ± 2.8
Hb (g·dL ⁻¹)	12.9 ± 2.7	13.2 ± 2.5	13.4 ± 2.7	12.7 ± 2.7	12.5 ± 2.5	13.4 ± 2.4	12.5 ± 2.6
SBE (mmol·L ⁻¹)	0.8 ± 0.3	0.9 ± 0.4	0.9 ± 0.3	0.7 ± 0.4	0.5 ± 0.3	0.4 ± 0.4	0.5 ± 0.3
SpO ₂ (%)	98.5 ± 0.8	98.3 ± 0.7	98.4 ± 0.8	98.2 ± 0.7	98.5 ± 0.4	98.4 ± 0.4	98.5 ± 0.5
Body Temperature (C)	36.5 ± 0.6	36.5 ± 0.7	36.4 ± 0.7	36.3 ± 0.8	36.3 ± 0.7	36.2 ± 0.8	36.2 ± 0.7

Data: mean ± SD.

HR: heart rate, SBP: systolic blood pressure, PaCO₂: arterial carbon dioxide tension

SBE: standard base excess

FIGURE 1 Continuous measurements of N₂, O₂ and N₂O fractional concentrations. Respiratory gas fractional concentration was continuously measured using the mass spectrometer. N₂ was quickly replaced with N₂O maintaining F_IO₂ at 0.33. (A) The decrease in N₂ concentration and reciprocal increase in N₂O concentration are shown after N₂O inhalation. Arrow indicates the start of N₂O inhalation. (B) A magnified trace of respiratory oxygen concentration in the same patient presented in (A). Arrow indicates the start of N₂O inhalation.

N₂O/oxygen. F_IO₂ was kept constant at 0.33 throughout the study period. The PaO₂ was measured at 1, 5, 10, 30, and 60 min using blood gas analyzer ABL 520 (Radiometer, Copenhagen, Denmark) and

hemodynamic variables including heart rate and systemic blood pressure were recorded simultaneously.

Statistical analysis

All variables were presented as mean ± SD. Data were analyzed by one-way analysis of variance (ANOVA) for repeated measures and Fisher's least significant difference technique. Differences were considered significant at $P < 0.05$.

Results

Table II shows hemodynamic blood gas analysis data before and after N₂O inhalation. There were no differences in heart rate or systemic blood pressure during the study. A small dose of fentanyl was administered to eight patients and ephedrine was used in three. Figure 1A shows a sample trace of respiratory gas fractional concentrations measured by RGMS on a breath-by-breath basis. Figure 1B shows a magnified trace of F_IO₂ and F_{ET}O₂ in the same recording. After N₂O inhalation, F_{ET}O₂ increased to maximal level within five minutes and then gradually decreased. Figure 2 shows the changes of F_IO₂ and F_{ET}O₂ measured by RGMS system before and after N₂O inhalation. Five minutes after the N₂O inhalation, F_{ET}O₂ increased from 0.27 ± 0.01 to 0.31 ± 0.02 ($n = 15$, $P < 0.01$). The PaO₂ significantly increased from 172.0 ± 22.5 mmHg to 201.0 ± 10.3 mmHg and correlated with the increase in F_{ET}O₂ at five minutes ($n = 15$, $P < 0.01$, Figure 3). The effects produced by N₂O inhalation on F_{ET}O₂ and PaO₂ were observed for at least 30 min.

Discussion

The findings of our study confirm the second gas effect on oxygen uptake in humans and provide the following information: (i) the PaO₂ increase correlated with the increase in F_{ET}O₂ after N₂O inhalation, (ii) the effects produced by N₂O on both PaO₂ and F_{ET}O₂

FIGURE 2 Changes in $F_I O_2$ (circle) and $F_{ET} O_2$ (triangle) before and after N_2O inhalation measured using respiratory gas mass spectrometer (RGMS). The transient decrease in $F_I O_2$ at one minute after N_2O inhalation might be the result of the delay in adjusting $F_I O_2$ at 0.33 in this system. Values are expressed as mean $\pm$ SD. $\dagger P < 0.01$, $* P < 0.05$ compared with baseline value.

FIGURE 3 Changes in PaO_2 after N_2O inhalation. Values are expressed as mean $\pm$ SD. $\dagger P < 0.01$, $* P < 0.05$ compared with baseline value.

were observed for 30 min. This is the first report to show continuous measurement of both inspiratory and alveolar (end-tidal) oxygen fractional concentrations after N_2O inhalation in patients under general anesthesia on a breath-by-breath basis.

Although recent publications have questioned the concept of the second gas effect in clinical practice,^{9,10} our results confirm and support the classical explanation of this concept. As for oxygen, Rackow *et al.*¹¹ predicted alveolar hyper-oxygenation during the induction of anesthesia, and Bojrab *et al.*¹² reported the increase in PaO_2 during N_2O inhalation. Our findings were consistent with these reports that first showed the increase in PaO_2 after the start of N_2O inhalation. Our results are also consistent with a recent study that demonstrated the existence of the second gas effect in humans using the new inhalation anesthetic, desflurane, in combination with N_2O .¹³ Desflurane has a blood/gas coefficient indistinguishable from that of N_2O . Thus, the rate of rise of the alveolar concentration should be the same for both desflurane and N_2O during their administration, regardless of the inspired concentrations. However, the administration of N_2O 65% increased the F_A/F_I ratio for both N_2O and concurrently administered desflurane relative to the administration of N_2O 5%, suggesting that the second gas effect results from the uptake of substantial volumes of N_2O .

Recently, Sun *et al.*⁹ reported that the second gas effect was not a valid concept. Although there are some experimental design differences between our study and theirs, our results do not support their suggestion. They administered N_2O 80% rather than 67% and showed that a high concentration of N_2O did not facilitate the rise of F_A/F_I during five minutes measurements. We do not know how the administration of N_2O 80% affects cardiac output, however, N_2O stimulates the central sympathetic nervous system as well as influencing pulmonary chemoreceptors. Cardiac output may also affect PaO_2 .¹⁴ We selected orthopedic patients in whom surgical stimulation was expected to be minimal and surgical stimulation was minimized by the additional fentanyl administration. In fact, no changes were observed in heart rate or systemic blood pressure during the study. Thus, we concluded that it was unlikely that changes in cardiac output were responsible for the changes in $F_{ET} O_2$ and PaO_2 , although we were unable to measure changes of cardiac output. We did not use any volatile anesthetic gas in this study. Therefore, FRC wash-in was eliminated. Finally, we tried to keep $F_I O_2$ constant at 0.33 throughout the study because a change in $F_I O_2$ affects both $F_{ET} O_2$ and PaO_2 . The $F_I O_2$ showed a small change immediately after N_2O inhalation due to the delay in adjusting oxygen fraction at 0.33 in several patients; however, it could be stabilized at 0.33 in a few minutes. Thus, we considered that changes in $F_I O_2$ were not responsible for the changes in $F_{ET} O_2$ and PaO_2 .

The changes in both $F_{ET}O_2$ (alveolar oxygen concentration) and PaO_2 after N_2O inhalation have not been demonstrated previously. We determined the relationship between $F_{ET}O_2$ and PaO_2 , and clearly showed that the PaO_2 increase correlated with the increase in $F_{ET}O_2$. As shown in Figure 2, $F_{ET}O_2$ one minute after N_2O inhalation was not different from baseline because of large variability. Sixty minutes after N_2O , the $F_{ET}O_2$ value was still higher than that of baseline, whereas PaO_2 had returned to control. We do not know if there are clinical implications for this difference or whether the difference arises from statistical problems.

In conclusion, our results confirm the concept of the second gas effect of N_2O on oxygen uptake in humans under general anesthesia in a breath-by-breath basis and that provide evidence that PaO_2 increase correlated with the increase in alveolar oxygen concentration after N_2O inhalation.

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