Transcranial doppler sonography: nitrous oxide and cerebral blood flow velocity in children

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To determine the effect of nitrous oxide (N_2O) on cerebral blood flow velocity (CBFV) and cerebrovascular resistance index ($RI+$) in children, ten ASA physical status I or II patients aged one to eight years old, scheduled for urological procedures, were studied. Anaesthesia was induced with thiopentone $2 \text{ mg} \cdot \text{kg}^{-1}$, fentanyl $5 \text{ } \mu\text{g} \cdot \text{kg}^{-1}$ and diazepam $0.3 \text{ mg} \cdot \text{kg}^{-1}$. Muscular relaxation was ensured by using vecuronium $0.1 \text{ mg} \cdot \text{kg}^{-1}$. After tracheal intubation, anaesthesia was randomly assigned to either a mixture of air in oxygen (N_2/O_2) or 70% N_2O in oxygen (N_2O/O_2) producing an FiO_2 of 30%. Three sets of measurements of CBFV and $RI+$ were made with both gas mixtures. The CBFV and $RI+$ were measured in the middle cerebral artery (MCA) with a transcranial Doppler monitor. Measurements were made while using the initial gas mixture, then the second gas mixture was administered, and finally, the patient again was given the initial gas mixture. A continuous caudal epidural or lumbar epidural block was performed before skin incision. Neuromuscular blockade was maintained with vecuronium $0.05 \text{ mg} \cdot \text{kg}^{-1}$. Temperature, heart rate, end-tidal CO_2 , arterial oxygen saturation, haematocrit and arterial blood pressure were maintained constant. Ventilation was adjusted to

achieve normocapnia. The CBFV increased when 70% N_2/O_2 was replaced by 70% N_2O/O_2 ($P < 0.05$) while the CBFV decreased when 70% N_2O/O_2 was readministered ($P < 0.05$). Likewise, the CBFV decreased when 70% N_2O/O_2 was replaced by 70% N_2/O_2 ($P < 0.05$) while the CBFV increased when 70% N_2O/O_2 was readministered ($P < 0.05$). The $RI+$, heart rate and blood pressure showed no change at any time during the study. These data indicate that N_2O , in clinical dosage, increases the CBFV in healthy children while the $RI+$ remains unchanged. These effects are probably due to the direct effect of N_2O on cerebral mitochondrial activity.

Afin de déterminer l'effet de l'oxide nitreux (N_2O) sur la vélocité du débit sanguin cérébral (CBFV) et sur l'index des résistances cérébrovasculaires ($RI+$), dix enfants âgés de deux à huit ans et ayant un état physique ASA I ou II et cédulés pour une chirurgie urologique ont été étudiés. L'induction de l'anesthésie était accomplie avec du thiopentone $2 \text{ mg} \cdot \text{kg}^{-1}$, fentanyl $5 \text{ } \mu\text{g} \cdot \text{kg}^{-1}$, et diazepam $0,3 \text{ mg} \cdot \text{kg}^{-1}$. La relaxation musculaire était assurée par du vecuronium $0,1 \text{ mg} \cdot \text{kg}^{-1}$. Après intubation endotrachéale, la maintenance anesthésique était aléatoirement choisie pour être débutée soit par l'utilisation d'air dans de l'oxygène (N_2/O_2) ou 70% N_2O dans de l'oxygène (N_2O/O_2) pour une FiO_2 de 30%. La CBFV et la $RI+$ était obtenue par mesure de l'artère cérébrale moyenne (MCA) avec une sonde Doppler transcranienne Doppler. La CBFV et la $RI+$ ont été mesurés pour chaque mélange utilisé. Après avoir obtenus CBFV et $RI+$ avec le mélange initial, l'autre mélange gazeux était administré et finalement, le patient recevait de nouveau le mélange initial. Une analgésie régionale lombaire ou caudale épidurale était performée avant le début de l'intervention chirurgicale. La température, le rythme cardiaque, la saturation en oxygène et la pression artérielle systolique étaient maintenus constants. La ventilation contrôlée par mode intermittent de pression positive était ajustée pour assurer la normocapnie. La CBFV a augmentée de 70% lorsque N_2O/O_2 était remplacé par le mélange N_2/O_2 ($P < 0,05$) pendant que la CBFV a diminuée de 70% lorsque N_2/O_2 était readministré ($P < 0,05$). Par ailleurs, la CBFV a diminuée de 70% lorsque la N_2O/O_2 était remplacé par N_2/O_2 ($P < 0,05$) pendant que la

Key words

ANAESTHESIA: paediatric;

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CBFV a augmentée de 70% lorsque N₂O/O₂ était réadministré ($P < 0,05$). La RI+ ainsi que le rythme cardiaque et la pression artérielle n'ont en aucun temps changés. Ces informations indique que N₂O en dose clinique augmente la CBFV chez les enfants anesthésiés pendant que la RI+ demeure inchangée. Ceci est une indication très probable d'un effet direct du N₂O sur l'activité mitochondrial cérébrale.

Despite substantial investigation, the effect of nitrous oxide (N₂O) on cerebral circulation remains controversial.¹ Pelligrino *et al.* showed an increase in cerebral blood flow (CBF) and cerebral oxygen consumption (CMRO₂) in goats given 70% N₂O.² Wollman *et al.* showed an increase in CBF and a decrease in CMRO₂ in adults given 70% N₂O.³ Theye and Michenfelder showed an 11% increase in CMRO₂ in dogs given N₂O.⁴ Carlsson *et al.* showed no change in CMRO₂ in rats given 70% N₂O.⁵ Sakabe *et al.* found an increase in CBF in adults given 60% N₂O, whereas in dogs given 60% N₂O they found an increase in CBF and CMRO₂ and no change in cerebrovascular resistance.^{6,7} Though the studies showed that N₂O caused an increase in CBF, many of the experiments were complicated by concurrent usage of halothane or isoflurane.⁸ As a result, there is no consensus on the true effect of N₂O on the cerebral blood flow and cerebrovascular resistance.

Hitherto, the measurement of CBF has been accomplished with invasive technology such as radiolabelled isotopes or cerebral angiography. Such methods are unsuitable for routine investigation in children. Recent advances in the field of ultrasound have made it possible to estimate CBF noninvasively. Transcranial Doppler sonography (TCD), a non-invasive technique described by Aaslid (1982) may be used to measure the velocity of blood flowing in the large basal cerebral arteries.⁹⁻¹¹ The adaptation of a 2 MHz Doppler allows insonation of intracerebral arteries through thin bone in older children and adults. Previously, intracranial arteries were inaccessible to Doppler-shifted ultrasound measurements except in neonates, infants, and young children with open fontanelles.

Due to the widespread use of N₂O in neurosurgical anaesthesia, it is important to know the cerebrovascular responses to N₂O in anaesthetized children. This study was undertaken using TCD to evaluate the effect of N₂O on cerebral blood flow velocity (CBFV) and cerebrovascular resistance index (RI+) in such patients.

Methods

Practical procedure

Following approval from our Human Subjects Review

Committee, written, informed consent was obtained from the parents of ten healthy ASA physical status I or II children, aged from one to eight years old, scheduled for elective urological surgery. All children were fasting and unpremedicated. Patients with cardiac or neurological disease or patients with contraindication to regional anaesthesia were excluded. All patients were supine and horizontal throughout the study.

Anaesthesia was induced with intravenous thiopentone 2 mg · kg⁻¹, fentanyl 5 µg · kg⁻¹, diazepam 0.3 mg · kg⁻¹, and vecuronium 0.1 mg · kg⁻¹. After tracheal intubation intermittent positive pressure ventilation was adjusted to achieve a PETCO₂ of 40 mmHg. Positive end-expiratory pressure was avoided. Fresh gas flow was maintained constant throughout the study to avoid changes in intrathoracic pressure. In a random fashion, anaesthesia was maintained with either a mixture of air in oxygen (N₂/O₂) or 70% N₂O/O₂ with an FiO₂ of 30%. Muscle relaxation was monitored by peripheral nerve stimulator and maintained with vecuronium 0.05 mg · kg⁻¹. A continuous caudal epidural or lumbar epidural block using 0.25% bupivacaine without epinephrine was administered to all patients before incision. Normothermia was maintained using a humidity and moisture exchanger (Gibeck-Dryden Corporation, Indianapolis, Indiana, USA)^{12,13} and a warming blanket.¹⁴ Lactated Ringer's solution (5 ml · kg⁻¹) was administered over the initial 15 min to compensate for preoperative fasting. All patients received 2 ml · kg⁻¹ · hr⁻¹ lactated Ringer's solution as maintenance fluid and additional fluid was given as needed to replace surgical losses. Systolic arterial blood pressure was measured by sphygmomanometer and Doppler ultrasonic transducer,¹⁵ heart rate, ET CO₂, arterial oxygen saturation, and inspired O₂ fractions were maintained at constant levels throughout the study. The end-tidal concentrations of N₂O and CO₂ were measured from the distal end of the tracheal tube and analyzed with a calibrated Puritan-Bennett Datex 254 airway gas monitor (Datex Instrumentation Corporation, Helsinki, Finland).¹⁶ The gas monitor was calibrated using a reference gas mixture before each use.

Fifteen-minute periods were allowed between N₂/O₂ or N₂O/O₂ changes to achieve steady-state conditions. After each period, the investigator (BB) who was unable to see the TCD screen, recorded three consecutive measurements of CBFV and RI+ in the MCA at one-minute intervals. Following these measurements, the patients received the alternate gas mixture and a further three measurements of CBFV and RI+ were recorded after the equilibration period. Finally, the patients received the original gas mixture and three measurements of CBFV and RI+ were again recorded. The CBFV and RI+ were recorded with a TCD (Transpect TCD, Medasonics,

TABLE Data summary

	N_2O/O_2	N_2/O_2	N_2O/O_2	N_2/O_2	N_2O/O_2	N_2/O_2	P^a	P^b
HR (beats/min ⁻¹)	81 ± 14	81 ± 16	80 ± 16	83 ± 7	81 ± 6	82 ± 7	NS	NS
SABP (mmHg)	87 ± 13	88 ± 14	86 ± 12	98 ± 15	98 ± 15	99 ± 16	NS	NS
ETCO ₂ (mmHg)	40 ± 2	39 ± 2	39 ± 1	39 ± 3	38 ± 2	38 ± 3	NS	NS
Temp (°C)	36.8	36.7	36.7	36.8	36.8	36.7	NS	NS
	±0.2	±0.2	±0.1	±0.1	±0.1	±0.2	NS	NS
AP (cmH ₂ O)	21 ± 3	20 ± 2	20 ± 3	22 ± 2	21 ± 3	20 ± 3	NS	NS
SaO ₂ (%)	98 ± 3	99 ± 2	99 ± 2	98 ± 3	97 ± 3	99 ± 1	NS	NS
CBFV (cm/sec ⁻¹)	108.4	101.4	109.1	97.9	107.9	96.9	<.05	<.05
	±23.4	±23.0	±21.9	±15.18	±27.3	±18.2		
RI+	0.66	0.66	0.68	0.67	0.67	0.64	NS	NS
	±.05	±.03	±.06	±.06	±.10	±0.06	NS	NS

All values are mean (SD), $n = 5$ /group.

Abbreviations: HR, heart rate; SABP, systolic arterial blood pressure; ETCO₂, end-tidal CO₂; TEMP, temperature; AP, airway pressure; SaO₂, arterial oxygen saturation; CBFV, cerebral blood flow velocity; RI+, cerebrovascular resistance.

^a P Values by one-way analysis of variance and Student Newman-Keuls for multiple comparisons within $N_2O/O_2 - N_2/O_2 - N_2O/O_2$.

^b P Values by repeated-measures of variance and Student Newman-Keuls for multiple comparisons within $N_2/O_2 - N_2O/O_2 - N_2/O_2$.

Fremont, CA) the specifications of which and the methodology of recording the MCA has been previously described.¹⁷ Systolic arterial blood pressure, heart rate, ETCO₂, arterial oxygen saturation, temperature, and FiO₂ were recorded with each steady-state measurement.

Statistical analysis

The mean ± standard deviation (SD) for age and weight were determined. The analysis of each TCD file was done by an investigator (BB) who was unaware of the gas mixture sequence at which each file was recorded. Each file represents eight seconds of recording from which an average from three cycles was obtained to evaluate the CBFV and to calculate the RI+. Based on a previous human adult study⁸ and for a power analysis of 0.80, an alpha value of 0.05 and a beta value of 0.20, the calculated number of patients needed to reject the null hypothesis was five per group. Repeated-measures analysis of variance and the Student Newman-Keuls test for multiple comparisons were used to determine the relationship within group (70% N₂O/O₂ or N₂/O₂) and CBFV, RI+, heart rate, systolic arterial blood pressure, ETCO₂, temperature and arterial oxygen saturation. A $P < 0.05$ was considered statistically significant.

Results

The mean ± SD age and weight of the ten children were 41.7 ± 27.9 mo and 15.5 ± 5.9 kg, respectively. Heart rate, systolic arterial blood pressure, ETCO₂, temperature, FiO₂, and arterial O₂ saturation did not change during the study period (Table). Doppler recordings of the CBFV in the MCA and calculations of RI+ values were

completed in all children for 70% N₂O/O₂ and for N₂/O₂ (Table).

The CBFV increased 9.9% when 70% N₂/O₂ was replaced by 70% N₂O/O₂ ($P < 0.05$). When 70% N₂/O₂ was readministered, CBFV returned to the initial value (Figure). Conversely, we found that the CBFV decreased 8.7% when 70% N₂O/O₂ was replaced by 70% N₂/O₂ ($P < 0.05$). When 70% N₂O/O₂ was readministered, CBFV returned to initial value (Figure). The RI+ did not change during any of the measurements. There were no complications from the use of the TCD in this study.

Discussion

We showed that 70% N₂O increased CBFV independent of any significant changes in cerebrovascular resistance index, systolic arterial blood pressure or heart rate. These data indicate that N₂O in clinical doses increases the CBFV in healthy children while RI+ remains unchanged. It is possible that N₂O may have a direct effect on the neurotransmitter activity of the vasomotor centre or an effect on mitochondrial cerebral metabolic activity with a resultant coupled increase in CBF without any sympathoadrenal responses.

Pelligrino *et al.* reported that in goats, N₂O/O₂ increased CBF with a parallel increase in CMRO₂ without any alterations in arterial blood pressure and heart rate. It was hypothesized that these results were attributed to direct effects of N₂O on cerebral metabolism and cerebral blood flow.² The authors measured serum catecholamine levels and high energy phosphate bonds (phosphocreatine, ATP, ADP, AMP, glucose-6-phosphate, fructose-6-phosphate lactate, and pyruvate) and showed that there

FIGURE Cerebral blood flow velocity (CBFV) recorded during gas mixture alteration between N_2O/O_2 and air/ O_2 (N_2/O_2). Values are reported as mean $\pm$ SD. * $P < 0.05$ compared with N_2O/O_2 before and after N_2/O_2 . + $P < 0.05$ compared with N_2/O_2 before and after N_2/O_2 .

was a decrease in serum catecholamines and no evidence of an increase in glycolytic intermediates. However, this did not eliminate the possible effect of N_2O on the brain redox function and cellular energy demand. Rosenthal *et al.* reported that in rats an increased oxidation of cytochrome a, a_3 , occurs during N_2O anaesthesia, suggesting an increased energy demand.¹⁸ Pelligrino *et al.* using a goat cerebrocortical mitochondrial preparation *in vitro*, observed that the increased O_2 utilization during exposure to N_2O may be due at least partly to a direct effect of N_2O on mitochondrial respiration.² Under normal conditions, the brain is dependent upon a continuous supply of blood in order to obtain a continuous flow of O_2 as well as glucose to the cells.¹⁹ Any alterations in the electron transport through the mitochondrial respiratory chain may result in a modification in O_2 utilization and a change in cerebral blood flow.¹⁹ It is permissible to speculate that N_2O , through a direct cellular effect, affects the electron transport of the inner membrane of the mitochondrion and decreased O_2 utilization by the respiratory chain, thus increasing cerebral blood flow. In this study measurement of the CBFV with both N_2O/O_2 and N_2/O_2 demonstrated an increase in CBFV with N_2O/O_2 . There was no change in RI+. This lack of change in the RI+ suggests a coupling of the CBF-CMRO₂ match. Todd *et al.* showed that N_2O causes a consistent increase in EEG frequency and a decrease in amplitude compared with N_2 .²⁰ Vernheit *et al.* reported that N_2O causes a 70% increase in CMRO₂ by its stimulating effect on the electrocortical activity as a secondary effect on brainstem reticular centers.²¹ Although we did not measure CMRO₂

or record EEG in this series of children, this cerebral excitatory state does not appear to be related to sympathetic activity. Several studies have reported that N_2O can increase sympathetic activity^{22,23} by an action originating from the suprapontine levels.²⁴ This would suggest that the possible increase in cerebral blood flow velocity was the result of sympathoadrenal stimulation. This study did not show any sign of increase in arterial blood pressure and/or heart rate while CBFV increased.

Kaieda *et al.* reported that no increase in CMRO₂ occurred due to N_2O anaesthesia. He suggested that the change in CBF with N_2O was not mediated by metabolic changes, but implied that N_2O may act as a direct cerebral vasodilator.²⁵ If our observations had shown that at a constant arterial blood pressure and heart rate, the effect of N_2O (expressed by a decrease in RI+) is to produce cerebral vasodilatation, we would have expected a decrease in CBFV. Since we found an increase in CBFV with no change in RI+ our study cannot support the findings of Kaieda.²⁵

Our methodology may be criticized insofar as we deepened anaesthesia by adding 70% N_2O . The magnitude of this effect varies considerably from study to study, but a recurring pattern suggests that the production of deeper anaesthesia may reduce the increase in CBF.⁸ Cerebral blood flow is directly proportional to the perfusion pressure gradient across the cerebral circulation in the brain and if the systolic arterial blood pressure decreases as the concentration of N_2O increases and anaesthesia deepens, we would expect CBFV to decrease. No changes in systolic arterial blood pressure or heart rate were found at any time during the study, but CBFV increased consistently when N_2O/O_2 was substituted for N_2/O_2 .

To reduce the surgical nociceptive stimulus and the sympathetic response to the incision and to limit the known effect of any changes of the arterial blood pressure and heart rate on the cerebral blood flow²⁶⁻²⁹ we performed a lumbar epidural or caudal block. Dohi *et al.* confirmed the clinical impression that children under six years old do not experience any change in arterial blood pressure and heart rate following spinal anaesthesia.³⁰ Delleur *et al.* reported the effects of epidural anaesthesia on 76 infants and children less than eight years old.³¹ In no case did any change in arterial blood pressure or heart rate occur. None of the patients in our study showed any changes in systolic arterial blood pressure or heart rate after administration of the regional anaesthesia.

The equilibration time constant for nitrous oxide in the grey matter of the brain is 0.47 min.³² In this study, when the airway gas monitor reached a stable 70% reading for the N_2O/O_2 group or a 0% reading indicating that N_2O

had been completely eliminated for the N₂/O₂ group, we delayed measurements for a further 15 min to ensure steady-state conditions within the brain. If the 15-min equilibration periods had been inadequate, then CBFV would have changed between the first and third measurements in an individual patient for any single set of conditions. However, the data showed a coefficient of variation of $\leq 7\%$ between the first and third recordings for any set of measurements.

Intrathoracic pressure affects cerebral perfusion pressure by its direct effect on venous return and therefore cerebral venous pressure. To maintain a constant mean intrathoracic pressure during the study we kept the respiratory rate and tidal volume constant, maintaining a PETCO₂ of about 40 mmHg. The arterial PCO₂ was estimated by measuring the PETCO₂ at the distal end of the endotracheal tube. Previous studies have shown that both single-breath and continuous distal PETCO₂ closely approximates PaCO₂ in healthy infants and children.^{16,33}

There are several methodological considerations that merit comment. The cerebral blood flow velocity and cerebrovascular resistance were measured by transcranial Doppler and several assumptions underly the relationship between CBFV and CBF.^{10,17} Moreover, other potential pitfalls in measurements which could account for large variations in measurement have been discussed in a previous paper.¹⁷

In summary we have shown that N₂O increases CBFV and although the mechanism is not known it is speculated that N₂O causes an increase in CBFV by a coupling of CBF-CMRO₂ probably because of a direct effect of N₂O on cerebral mitochondrial activity. These findings are consistent with previous investigations on the effect of N₂O on CBF. The clinical implications remains unclear.²⁰ Before applying this observation to clinical paediatric anaesthetic practice, further studies are required. These would include measurement of mitochondrial cellular activity to determine the true effect of N₂O on the mitochondrial respiratory chain and O₂ utilization.

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