Cerebrovascular responses to carbon dioxide in children anaesthetized with halothane and isoflurane

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To determine the effects of isoflurane and halothane on cerebrovascular reactivity to CO_2 , 30 children aged one to six years were anaesthetized with isoflurane or halothane in an air and oxygen mixture with an FiO_2 of 0.3. The end-tidal concentrations (0.5 minimum alveolar concentration (MAC) or 1.0 MAC) of isoflurane or halothane were age-adjusted. After achieving a steady-state at both 0.5 MAC and 1.0 MAC isoflurane and halothane, the end-tidal carbon dioxide tension (PETCO_2) was randomly adjusted to 20, 40, or 60 mmHg. Cerebral blood flow velocity (CBFV) and the cerebrovascular resistance index ($\text{RI}+$) in the middle cerebral artery (MCA) were measured by a transcranial Doppler monitor. Three measurements of CBFV and $\text{RI}+$ were obtained at each PETCO_2 and isoflurane or halothane concentration. Any rise in the PETCO_2 caused an increase in CBFV during both 0.5 MAC ($r^2 = 0.99$ and 0.99) and 1.0 MAC ($r^2 = 0.96$ and 0.95) isoflurane and halothane anaesthesia, respectively ($P < 0.05$). The CBFV for isoflurane increased as PETCO_2 increased from 20 to 60 mmHg for both 0.5 MAC and 1.0 MAC ($P < 0.05$). The CBFV for halothane increased as PETCO_2 increased from 20 to

40 mmHg for both 0.5 MAC and 1.0 MAC halothane ($P < 0.05$), but did not change as PETCO_2 increased from 40 to 60 mmHg for both 0.5 MAC and 1.0 MAC halothane. The $\text{RI}+$ showed an inverse relationship with CBFV at each PETCO_2 for 0.5 MAC ($r^2 = 0.98$ and 0.99) and 1.0 MAC ($r^2 = 0.76$ and 0.53) isoflurane and halothane, respectively ($P < 0.05$). The CBFV did not differ significantly between 0.5 and 1.0 MAC isoflurane and halothane at corresponding PETCO_2 values. The cerebrovascular response to CO_2 at 20 mmHg between 0.5 MAC and 1.0 MAC halothane was not significantly different. These data strongly suggest that isoflurane and halothane in doses up to 1.0 MAC do not affect the cerebrovascular reactivity of the MCA to CO_2 in anaesthetized, healthy children.

Key words

ANAESTHESIA: paediatric;
ANAESTHETICS, VOLATILE: isoflurane, halothane;
BRAIN: cerebral blood flow;
CARBON DIOXIDE: tension, end-tidal;
MEASUREMENT TECHNIQUE: transcranial Doppler.

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Afin de déterminer l'effet de l'isoflurane et de l'halothane sur la réactivité du système cérébrovasculaire au dioxyde de carbone (CO_2), 30 enfants âgés de un à six ans anesthésiés avec de l'isoflurane ou de l'halothane dans un mélange d'air et d'oxygène à une concentration inspirée de 0.3 ont été utilisés. Les concentrations en fin expiratoire (0.5 concentration alvéolaire minimum (MAC) ou 1.0 MAC) d'isoflurane ou d'halothane étaient ajustées pour l'âge. Après avoir obtenu l'état d'équilibre à 0.5 MAC et 1.0 MAC pour chacun des gaz, la tension en fin d'expiration du CO_2 (PETCO_2) était de façon aléatoire ajustée à 20, 40, et 60 mmHg. La vitesse du débit sanguin cérébral (CBFV) ainsi que l'index de résistance cérébrovasculaire ($\text{RI}+$) de l'artère moyenne cérébrale (MCA) ont été mesurés au moyen d'un Doppler transcranien. Trois mesures de CBFV et $\text{RI}+$ étaient obtenus pour chacune des PETCO_2 aux différentes concentrations d'isoflurane et d'halothane étudiées. Nous avons observé que la CBFV augmentait de façon logarithmique avec l'augmentation de la PETCO_2 pour chacun des volatiles et ce, à 0.5 MAC ($r^2 = 0.99$ et 0.99) ($P < 0.05$) ainsi qu'à 1.0 MAC ($r^2 = 0.96$ et 0.95) ($P < 0.05$) respectivement. La CBFV pour l'isoflurane à 0.5 MAC et 1.0 MAC a augmenté significativement lorsque la PETCO_2 augmentait de 20 à 60 mmHg ($P < 0.05$). La CBFV pour l'halothane à 0.5 MAC et 1.0 MAC augmentait significativement seulement lorsque la PETCO_2 passait de 20 à 40 mmHg ($P < 0.05$) pendant aucune

augmentation supplémentaire était notée lorsque la $PETCO_2$ passait de 40 à 60 mmHg. La $RI+$ a montré pour chacun des agents utilisés une relation logarithmique inverse à celle de la CBFV en fonction de la $PETCO_2$ à 0.5 MAC ($r^2 = 0.98$ et 0.99) ($P < 0.05$) et 1.0 MAC ($r^2 = 0.76$ et 0.53) ($P < 0.05$) respectivement. La CBFV n'a pas différé significativement pour l'isoflurane ou l'halothane à 0.5 MAC ou 1.0 MAC et ce, à chaque niveau $PETCO_2$ étudiées. La réponse cérébrovasculaire observée à 20 mmHg $PETCO_2$ entre l'halothane 0.5 MAC et 1.0 MAC n'était pas statistiquement significative ($P = 0.056$). Ces résultats indiquent que l'isoflurane et l'halothane en concentration inspirées jusqu'à 1.0 MAC n'affectent pas la réactivité cérébrovasculaire de la MCA au CO_2 chez des enfants sains et anesthésiés.

Transcranial Doppler sonography (TCD) is a non-invasive technique that measures the velocity of blood flowing in the large basal cerebral arteries.¹⁻³ Hitherto, intracranial vessels were inaccessible to Doppler-shifted ultrasound measurements except in neonates and young infants. However, recently developed physical modifications have enabled measurement of middle cerebral artery (MCA) flow velocity through the temporal bone in anaesthetized children.²

Several factors affect cerebral blood flow (CBF) during anaesthesia including the carbon dioxide (CO_2) tension and the presence of volatile anaesthetics. Carbon dioxide directly affects the cerebral circulation by dilating the cerebral vessels and increasing cerebral blood flow.^{2,14} Carbon dioxide rapidly equilibrates across biological membranes and alters the perivascular pH. Since the perivascular pH is an important determinant of cerebrovascular reactivity, CO_2 exerts a rapid and considerable effect on CBF.³ Indeed, CBF varies directly and linearly with the $PaCO_2$ between CO_2 partial pressures of 20–60 mmHg, in adults, while Pilato *et al.* showed a logarithmic relationship between CBFV and $PaCO_2$ over the same range.^{2,3}

Halothane is an excellent anaesthetic agent for children and is thus widely used in clinical paediatric practice. It is commonly used in combination with hyperventilation in paediatric neuroanaesthesia. A recent TCD study demonstrated a hysteresis phenomenon in children anaesthetized with up to 1.5 MAC halothane.⁴ This finding could be important in patients with raised intracranial pressure. In animal studies halothane has been shown to decrease cerebrovascular resistance, increase cerebral blood flow and increase intracerebral pressure.⁵ Many human studies have supported these findings.⁶⁻⁹ Drummond *et al.* reported that the presence of hypocapnia resulted in a smaller reduction in cerebral blood flow (CBF) during the administration of halothane- N_2O than with isoflurane-

N_2O .¹⁰ Madsen *et al.* suggested that if thiopentone is used for induction and hypocapnia is established before the administration of 1.0 MAC halothane, cerebrovascular reactivity to a low $PaCO_2$ is maintained.⁵ If hypocapnia is not established initially, halothane is believed to have the propensity to attenuate the cerebrovascular vasoconstrictive effect of a low $PaCO_2$.⁹⁻¹¹

Isoflurane is considered to be the inhalational agent of choice in neuroanaesthesia because it dilates the cerebral vasculature to a lesser extent than halothane. We have demonstrated that the cerebral blood flow velocity (CBFV) and cerebrovascular resistance index ($RI+$) are constant during the administration of varying concentrations of isoflurane administered in a loop fashion to normocapnic children.¹² Similar results were obtained in adult studies in which isoflurane concentrations up to 1 MAC had a minimal effect on CBF.¹³

In this paper the effects of CO_2 between 20 and 60 mmHg on the CBFV and $RI+$ in healthy children anaesthetized with either isoflurane or halothane at 0.5 MAC and 1.0 MAC concentrations are reported.

Methods

Practical procedure

Following approval from the Human Subjects Review Committee, written and informed consent was obtained from the parents of 30 healthy ASA physical status I or II children aged one to six years old scheduled for elective urological surgery. All children were fasting and unpremedicated. Patients with cardiac or neurological disease or patients with a contraindication to regional anaesthesia were excluded. All patients were supine and horizontal throughout the study.

After application of the usual monitoring, anaesthesia was induced with intravenous thiopentone $5 \text{ mg} \cdot \text{kg}^{-1}$, fentanyl $2 \text{ } \mu\text{g} \cdot \text{kg}^{-1}$, and vecuronium $0.1 \text{ mg} \cdot \text{kg}^{-1}$. After tracheal intubation, intermittent positive pressure ventilation was established with peak inspiratory pressures maintained at 20–25 mmHg and positive end-expiratory pressure at zero. Ventilation was adjusted to achieve a $PETCO_2$ of 20 mmHg. A constant fresh gas flow was maintained throughout the study to avoid any changes in intrathoracic pressure. Anaesthesia was maintained with isoflurane or halothane in a mixture of air and oxygen to produce an FiO_2 of 0.3. Vecuronium $0.05 \text{ mg} \cdot \text{kg}^{-1}$ was used for muscle relaxation. A continuous caudal or lumbar epidural block using 0.25% bupivacaine without epinephrine was administered to all patients before the surgical incision.

Normothermia was maintained using a heat and moisture exchanger (Gibeck-Dryden Corporation, Indianapolis, Indiana, USA) and a warming blanket.¹⁵⁻¹⁷ Lactated

Ringer's solution (5 ml · kg⁻¹) was administered over the initial 15 min to replace the fluid deficit due to the fasting period. All patients received 2 ml · kg⁻¹ · hr⁻¹ lactated Ringer's solution as maintenance fluid and additional lactated Ringer's as needed to replace blood or surgical losses. The end-tidal concentrations of isoflurane, halothane 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).¹⁸ The gas monitor was calibrated using a reference gas mixture before each use.

The initial end-tidal concentration of isoflurane was randomized to either 0.5 MAC or 1.0 MAC. The concentration of halothane was set at 0.5 MAC because of its hysteresis effects.⁴ Three measurements of CBFV and RI+ were recorded at each CO₂ and isoflurane or halothane MAC value. Following these measurements, patients were equilibrated to the other concentration of isoflurane or 1.0 MAC halothane. Once again, three measurements of CBFV and RI+ were made at each CO₂ and isoflurane or halothane MAC value.

Doppler measurements were recorded after 15 min of steady-state isoflurane or halothane concentration. The PETCO₂ was then adjusted randomly to either 20, 40, or 60 mmHg by titrating exogenous CO₂ into the anaesthetic circuit. The end-tidal CO₂ was held constant for five minutes, after which the anaesthetist who was unable to see the TCD screen, recorded three consecutive measurements of CBFV and RI+ in the MCA at one-minute intervals. Systolic arterial pressure, heart rate, arterial oxygen saturation, temperature, inspired O₂ fraction and end-tidal isoflurane or end-tidal halothane concentrations were recorded simultaneously.

Doppler instrumentation

The TCD monitor (Transpect TCD Medasonics, Canada) used to determine CBFV and RI+ had the following characteristics: emitted ultrasonic frequency – 2 MHz; emitting area – 1.5 cm²; effective depth range – 25–120 mm; and emitted ultrasonic power – 100 mW. The frequency spectra of the Doppler signals were displayed on a real time spectrum analyzer (Medasonics 1024S) which allowed clear aural and visual separation of flow for unambiguous interpretation of the CBFV waveform.

The range-gated pulsed TCD probe was placed over the temporal window of the skull just cephalad to the zygomatic arch approximately 1–2 cm anterior to the tragus. The gate depth was set to 30–35 mm, initially, depending on the size of the patient according to the recommendations of Gillard *et al.*¹⁹ The Doppler signal was optimized for clear and accurate determinations by adjusting the gate depth, angle of insonation, power, and

dynamic range. Once positioned, the TCD probe was fixed in place with a modified Mayo Ether Screen that allowed for continuous measurements of CBFV and RI+ in the MCA without affecting either the location of the probe or the angle of insonation.

Three CBFV, RI+ and graphic displays of systolic and diastolic flow velocities were obtained during haemodynamic steady-state periods at each PETCO₂ for both the isoflurane and halothane concentrations studied. The Doppler frequency spectrum was displayed on a frequency analyzer and analyzed by fast Fourier transformation. The outline or envelope of the spectra was used to determine the CBFV within the MCA by positioning the cursor consecutively on three individual frequency outlines and averaging them. Fourier analysis provided a precise analysis based on the first or second harmonic of the cardiac cycle. The pulsatility index (RI+) was calculated from the mean of three displayed waveforms. The cerebrovascular resistance RI+ was calculated for each MCA velocity measurement according to the formula:

$$RI+ = (f_{\text{syst}} - f_{\text{dias}})/f_{\text{syst}}$$

where f_{syst} is the maximum frequency at the peak systole, and f_{dias} is the maximum frequency at end diastole, calculated for a selected complete cardiac cycle, as adapted from Pourcelot's index of resistance.²⁰

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 sequence and the anaesthetic agent at which each file was recorded. Based on a previous study¹⁰ we expected a difference between halothane and isoflurane in the hypocapnic patient. With 15 patients per group and an alpha value 0.05 the power to detect such a difference in the cerebrovascular reactivity with halothane versus isoflurane is 0.80. The relationships between the PETCO₂ and both the CBFV and RI+ were determined using a non-linear regression analysis. The dependence of both TCD variables on the PCO₂ was calculated using the coefficient of determination (r^2). Repeated measures analysis of variance and the Student Newman-Keuls test for multiple comparisons were used to determine within group (isoflurane or halothane) PETCO₂ effects and differences in CBFV, RI+, heart rate, systolic arterial pressure, temperature and arterial oxygen saturation. The unpaired *t* test was used for between group isoflurane and halothane comparisons at similar PETCO₂ levels. A *P* < 0.05 was considered statistically significant.

TABLE I Data summary (halothane)

	Hypocapnia			Normocapnia			Hypercapnia			P^b	
	$ET_{hal}0.5$	$ET_{hal}1.0$	P^a	$ET_{hal}0.5$	$ET_{hal}1.0$	P^a	$ET_{hal}0.5$	$ET_{hal}1.0$	P^a	0.5	1.0
HR (beats/min)	91±25	91±15	ns	93±22	88.5±20	ns	94±18	93±16	ns	ns	ns
SABP (mmHg)	79±11	76±12	ns	81±11	78±14	ns	81±10	79±13	ns	ns	ns
ETCO ₂ (mmHg)	20±2	21±2	ns	40±3	40±2	ns	59±2	60±3	ns	ns	ns
SaO ₂ (%)	98±2	99±3	ns	99±2	99±1	ns	99±2	98±2	ns	ns	ns
AP (cmH ₂ O)	21±3	22±4	ns	20±2	19±4	ns	21±4	22±3	ns	ns	ns
Temp (°C)	36.5 ±0.3	36.7 ±0.2	ns	36.6 ±0.2	36.7 ±0.2	ns	36.5 ±0.3	36.6 ±0.2	ns	ns	ns
CBFV (cmsec ⁻¹)	82.6 ±30.6	105.27 ±32.29	0.056	130.33 ±37.8	134.13 ±33.54	ns	140.0 ±39.4	143.47 ±39.01	ns	<0.05*	<0.05†
RI+	0.64 ±0.06	0.66 ±0.09	ns	0.63 ±0.10	0.61 ±0.05	ns	0.60 ±0.10	0.63 ±0.08	ns	ns	ns

All values are mean (SD), $n = 15$ /group.

Abbreviations: $ET_{hal}0.5$, end-tidal halothane 0.5 MAC; $ET_{hal}1.0$, end-tidal halothane 1.0 MAC; $ET_{iso}0.5$, end-tidal isoflurane 0.5 MAC; $ET_{iso}1.0$, end-tidal isoflurane 1.0 MAC; HR, heart rate; SABP, systolic arterial blood pressure; SaO₂, arterial oxygen saturation; Temp, body temperature; AP, airway pressure; CBFV, cerebral blood flow velocity; RI+, cerebrovascular resistance.

^a P values obtained by unpaired t test between both MAC at comparable ETCO₂.

^b P values are obtained by repeated-measures of variance and Student Newman-Keuls for multiple comparisons within each MAC for all three levels of ETCO₂.

*Comparing $ET_{hal}0.5$ MAC at ETCO₂ 40 with 20 mmHg ($P < 0.01$); 60 with 20 mmHg ($P < 0.05$); 60 with 40 mmHg ($P = NS$).

†Comparing $ET_{hal}1.0$ MAC at ETCO₂ 40 with 20 mmHg ($P < 0.001$); 60 with 20 mmHg ($P = 0.001$); 60 with 40 mmHg ($P = NS$).

FIGURE 1 Cerebral blood flow velocity (CBFV) versus PETCO₂. $P < 0.05$ compared with 20 mmHg* and 40 mmHg*.

Results

Age and weight did not differ between the isoflurane and halothane groups. The mean $\pm$ SD ages and weights of the 15 children in each group were 39.4 ± 27.2 mo and 15.5 ± 6.2 kg for isoflurane, and 41.7 ± 27.9 mo and 15.5 ± 5.9 kg for halothane. Heart rate, systolic arterial blood pressure, ETCO₂, arterial oxygen saturation, airway pressure, and temperature did not change between 0.5 and 1.0 MAC for halothane (Table I) and for isoflurane (Table II) during the study period. Doppler recordings of the CBFV in the MCA and calculations of RI+ values were completed in all children at 0.5 MAC

FIGURE 2 Cerebral blood flow velocity (CBFV) and cerebrovascular resistance index (RI+) for isoflurane versus PETCO₂. Values are mean ($\pm$ SD) for 15 subjects at each PETCO₂ value. Lines represent the non-linear regression fits for the CBFV and RI+ versus PETCO₂. The CBFV increased versus PETCO₂ at 0.5 MAC ($r^2 = 0.99$) and at 1.0 MAC ($r^2 = 0.96$). The RI+ decreased versus PETCO₂ at 0.5 MAC ($r^2 = 0.98$) and 1.0 MAC ($r^2 = 0.76$).

and 1.0 MAC halothane (Table I) and isoflurane (Table II) at each of the three PETCO₂ values.

We found that the CBFV increased significantly as PETCO₂ increased from 20 to 40 mmHg ($P < 0.001$) and from 40 to 60 mmHg ($P < 0.05$) at 0.5 MAC and from 20 to 40 mmHg ($P < 0.001$) and 40 to 60 mmHg ($P < 0.05$) at 1.0 MAC isoflurane (Figure 1). However, CBFV did

TABLE II Data summary (isoflurane)

	Hypocapnia			Normocapnia			Hypercapnia			<i>P</i> ^b	
	<i>ET</i> _{iso} 0.5	<i>ET</i> _{iso} 1.0	<i>P</i> ^a	<i>ET</i> _{iso} 0.5	<i>ET</i> _{iso} 1.0	<i>P</i> ^a	<i>ET</i> _{iso} 0.5	<i>ET</i> _{iso} 1.0	<i>P</i> ^a	0.5	1.0
HR (beats/min)	93±17	95±14	ns	100±14	97±14	ns	99±20	93±13	ns	ns	ns
SABP (mmHg)	84±10	81±10	ns	86±10	82±9	ns	89±11	85±10	ns	ns	ns
ETCO ₂ (mmHg)	21±2 *	21±3	ns	39±3	40±2	ns	60±2	61±2	ns	ns	ns
SaO ₂ (%)	99±2	99±3	ns	99±2	98±3	ns	97±3	98±2	ns	ns	ns
AP (cmH ₂ O)	22±3	22±4	ns	20±2	21±4	ns	22±4	22±3	ns	ns	ns
Temp (°C)	36.6	36	ns	36.6	36.4	ns	36.7	36.6	ns	ns	ns
	±0.2	±0.2		±0.2	±0.3		±0.3	±0.2			
CBFV (cmsec ⁻¹)	76.6	79.82	ns	115.64	121.28	ns	141.1	139.03	ns	<0.05*	<0.05†
	±17.5	±20.93		±28.69	±20.93		±23.36	±22.02			
RI+	0.79	0.83	ns	0.66	0.66	ns	0.62	0.69	ns	ns	ns
	±0.11	±0.1		±0.07	±0.05		±0.06	±0.05			

All values are mean (SD), *n* = 15/group.

Abbreviations: *ET*_{hal}0.5, end-tidal halothane 0.5 MAC; *ET*_{hal}1.0, end-tidal halothane 1.0 MAC; *ET*_{iso}0.5, end-tidal isoflurane 0.5 MAC; *ET*_{iso}1.0, end-tidal isoflurane 1.0 MAC; HR, heart rate; SABP, systolic arterial blood pressure; SaO₂, arterial oxygen saturation; Temp, body temperature; AP, airway pressure; CBFV, cerebral blood flow velocity; RI+, cerebrovascular resistance.

^a*P* values obtained by unpaired *t* test between both MAC at comparable ETCO₂.

^b*P* values are obtained by repeated-measures of variance and Student Newman-Keuls for multiple comparisons within each MAC for all three levels of ETCO₂.

*Comparing *ET*_{hal}0.5 MAC at ETCO₂ 40 with 20 mmHg (*P* < 0.01); 60 with 20 mmHg (*P* < 0.05); 60 with 40 mmHg (*P* = NS).

†Comparing *ET*_{hal}1.0 MAC at ETCO₂ 40 with 20 mmHg (*P* < 0.001); 60 with 20 mmHg (*P* = 0.001); 60 with 40 mmHg (*P* = NS).

FIGURE 3 Cerebral blood flow velocity (CBFV) versus PETCO₂. *P* < 0.05 compared with 20 mmHg* and 40 mmHg[†].

not differ significantly between 0.5 MAC and 1.0 MAC isoflurane at corresponding PETCO₂ values. The CBFV increased as PETCO₂ increased during both 0.5 MAC (*r*² = 0.99) and 1.0 MAC (*r*² = 0.96) isoflurane (*P* < 0.05). The RI+ showed the reverse relationship observed with CBFV when PETCO₂ increased at both 0.5 MAC (*r*² = 0.98) and 1.0 MAC (*r*² = 0.76) isoflurane (*P* < 0.05) (Figure 2).

The CBFV increased significantly as PETCO₂ increased from 20 to 40 mmHg (*P* = 0.007) at 0.5 MAC and

FIGURE 4 Cerebral blood flow velocity (CBFV) and cerebrovascular resistance index (RI+) for halothane versus PETCO₂. Values are mean (± SD) for 15 subjects at each PETCO₂ values. Lines represent the non-linear regression fits for the CBFV and RI+ versus PETCO₂. The CBFV increased versus PETCO₂ at 0.5 MAC (*r*² = 0.99) and at 1.0 MAC (*r*² = 0.95). The RI+ decreased versus PETCO₂ at 0.5 MAC (*r*² = 0.99) and 1.0 MAC (*r*² = 0.53).

from 20 to 40 mmHg (*P* < 0.001) at 1.0 MAC halothane (*P* < 0.05), but did not change as PETCO₂ increased from 40 to 60 mmHg for both 0.5 MAC and 1.0 MAC halothane (Figure 3). The CBFV did not differ between 0.5 MAC and 1.0 MAC halothane at the three PETCO₂ values. The CBFV increased as PETCO₂ increased during

both 0.5 MAC ($r^2 = 0.99$) and 1.0 MAC ($r^2 = 0.95$) halothane ($P < 0.05$). The RI+ decreased as PETCO₂ increased at both 0.5 MAC ($r^2 = 0.99$) and 1.0 MAC ($r^2 = 0.53$) halothane ($P < 0.05$) (Figure 4).

There were no complications from the use of the TCD in this study.

Discussion

The results of this investigation strongly suggest that isoflurane and halothane in doses up to 1.0 MAC do not affect the cerebrovascular reactivity of the MCA to CO₂ in anaesthetized, healthy children. Earlier investigations in animals and in adult humans produced contradictory results with regard to the effect of CO₂ on the cerebrovasculature especially during halothane anaesthesia.⁶⁻⁹ However, studies on cerebrovascular reactivity to CO₂, during isoflurane anaesthesia were consistent.⁹⁻¹⁰

The results of the present study failed to show an adverse effect of halothane (0.5 MAC or 1.0 MAC) on cerebrovascular reactivity to CO₂ when different CO₂ concentrations were introduced after halothane. Wollman *et al.*⁶ reported that during halothane anaesthesia, arterial PCO₂ levels affect cerebrovascular resistance and CBF in the same manner as in the non-anaesthetised man. Their findings are similar to ours for patients with normocapnia and hypocapnia. However, they did not study the magnitude of the vasoconstrictive response to hypocapnia.⁶ This present study shows that the cerebrovascular response between 0.5 MAC and 1.0 MAC halothane, even at 20 mmHg PETCO₂, was preserved. Many recent studies have suggested that halothane produces cerebral vasodilatation either by intracellular alteration of cyclic-AMP,²¹ decreased calcium accumulation in the sarcoplasmic reticulum,²² or by interacting with an endothelium-derived relaxing factor.²³ Manohar *et al.* reported that during halothane-O₂ anaesthesia, vasodilatation occurred in all regions of the brain.²⁴ Their study showed that cerebral blood flow increased from values obtained at 0.5 MAC halothane to reach a maximum at 1.5 MAC halothane whereas the cerebral vascular resistance decreased to its lowest value at 1.0 MAC halothane.²⁴ We have observed that between normocapnia and hypercapnia either at 0.5 MAC or at 1.0 MAC halothane concentrations no additional vasodilatation was caused by increasing the level of CO₂. This may suggest that halothane causes a maximal degree of cerebral vasodilatation and that subsequent increases in PaCO₂ do not increase vasodilatation. Lazzell *et al.* using a similar anaesthetic technique reported that at normocapnia CBFV and RI+ changed between 0.5 MAC and 1.0 MAC but they failed to show any further changes at 1.5 MAC.²⁵ They also observed that in spite of decreasing the halothane concentration from 1.5 MAC to 0.2 MAC, an

increased cerebral blood flow velocity was maintained for approximately 30–45 min⁴ – an hysteresis phenomenon. Based on their observations we did not randomize the halothane concentrations. Our results suggest that halothane has as potent a vasodilating effect as CO₂.

Cerebrovascular reactivity to hypocapnia has been shown to be more pronounced during isoflurane than during halothane anaesthesia in animals.¹⁰ The results reported in this paper are in agreement with the previously observed effects of isoflurane on CBF and cerebrovascular responses to CO₂ obtained in dogs^{10,26} and in adults anaesthetized with isoflurane.²⁷ It was interesting to observe with isoflurane that, between each level of CO₂ studied, a statistical difference in CBFV was measured. Pilato *et al.* demonstrated, at 1 % end-tidal isoflurane, a logarithmic relationship between 20 mmHg and 60 mmHg PETCO₂ and the CBFV of the MCA.² This suggests that the cerebrovascular dilatation observed in this study is related principally to the effect of CO₂ and not to the variation in isoflurane concentrations. In addition, Leon *et al.* showed that during normocapnia, varying the concentration of isoflurane between 0.5 MAC and 1.0 MAC in a loop fashion, did not change CBFV of the MCA.¹² They were unable to show any time–response effect of 1.0 MAC of isoflurane on CBFV of the MCA in anaesthetized children over 90 min. These results are similar to those of Algotsson *et al.* and Eintrei *et al.* at similar concentrations of isoflurane in adults.^{27,28}

Arterial PCO₂ was estimated by measuring the end-tidal CO₂ at the tip of the tracheal tube. Previous studies have shown that both single-breath and continuous distal PETCO₂ closely approximates PaCO₂ in healthy infants and children.^{18,29} The time constant for the equilibration of alveolar and arterial CO₂ is one minute.³⁰ We waited for five minutes at each CO₂ tension to ensure complete cerebral arteriolar response to CO₂. The equilibration time constant in cerebral grey matter for isoflurane and halothane is 1.4 and 2.4 min, respectively.³¹ We waited for 15 min to achieve steady-state conditions within the brain. The data showed no consistent changes between the first and third measurements at each concentration. It was concluded that the equilibration periods used for CO₂, isoflurane, and halothane produced steady-state conditions within the basal cerebral arteries.

The cerebrovascular response to PCO₂ has been shown to depend in part on the arterial blood pressure.^{32,33} Neither heart rate nor systolic arterial pressure changed at any time during the study. If the systolic arterial pressure had decreased as the concentration of isoflurane or halothane was increased then CBFV would have decreased providing that the arterial diameter remained unchanged. However, we found that CBFV did not change between 0.5 MAC and 1.0 MAC isoflurane. An

electrical model of the systemic arterial system has been used to demonstrate that the CBFV and resistance index RI+ is likely to be affected by changes in heart rate and arterial blood pressure.³⁴ Since systolic arterial pressure and heart rate did not change we believe that the changes observed in CBFV and RI+ were due to PCO₂.

Intrathoracic pressure alters the cerebral perfusion pressure by a direct effect on the cerebral venous pressure. A constant mean intrathoracic pressure was maintained during each study to isolate the effect of changes in ventilation on CBFV. The PETCO₂ was adjusted from an initial PETCO₂ of 20 mmHg produced by hyperventilation by the addition of exogenous CO₂ without altering the ventilator settings. Thus, the observed changes in CBFV at different PETCO₂ values could not be attributed to changes in intrathoracic pressure and/or venous return.

Interindividual variability could introduce error in the measurements. Each individual has a unique CBFV (an estimate of CBF) and this is determined by many factors such as metabolic demand, physiological state, blood pressure, blood properties and pathologic state. In fact, age is the major determinant of the CBFV. There is a linear increase in CBFV from birth to age two months. Thereafter it increases more slowly to reach a peak at six years old and then decreases slowly to 70% of this peak value at the age of 16. The CBFV then decreases an additional 20% between 20 and 60 yr of age.^{35,36}

Patients in this study all had similar haemoglobin concentrations (12–14 mg·dl⁻¹), metabolic demands (normothermia was maintained), and haemodynamic profiles (no change in blood pressure or heart rate at any time). The large standard deviations seen could therefore be explained by the range of ages of patients studied in this series (1–8 yr).

There are several methodological considerations that merit comment. The cerebral blood flow (CBF) and cerebrovascular resistance were measured by transcranial Doppler and several assumptions underly the relationship between CBFV and CBF. Four assumptions have to be made in regard to the TCD methodology before recording the CBFV in the MCA. They have been previously described.² Other potential pitfalls in measurements which could account for large standard deviations include errors based on the physics of sound waves and Doppler instruments. These include (a) an inability to separate adjacent vessels high pass filters designed to cut off low frequencies, noise or signals from wall motion, inadequate sampling frequency, (b) quality and adjustment of the Doppler equipment (problems due to low sensitivity to weak signals, absence of adequate filtering and insufficient precision of alignment), (c) an inadequate examination technique (operator error, large angle of insonation), anatomy of the brain vasculature, blood rheology (low

viscosity gives high CBFV), and interpretation of Doppler spectra.³⁷ All mentioned pitfalls may be avoided by an experienced examiner and are believed to be of little importance. The changes in TCD blood flow velocity reflect concomitant changes in CBF. Studies in humans and animals show a close correlation between changes in TCD velocity and CBF both in response to CO₂ and following treatment with anaesthetics and narcotics.³⁸ Several TCD studies have suggested that changes in velocity are proportional to changes in flow.^{39–41} However, absolute CBF values cannot be inferred from TCD data since the diameter of the insonated vessel segment remains unknown. Giller *et al.*⁴² reported the calibre of the large cerebral arteries in adult humans undergoing craniotomy does not change during variations in blood pressure and PCO₂. They showed that the calibre of the proximal cerebral arteries does not change but the small arterial branches may change diameter during pressure changes. Although the major part of cerebral vascular regulation occurs on the level of the resistance vessels,⁴³ further paediatric investigations involving classical CBF measurements and TCD are necessary to determine if intracranial vessel diameter changes. Until then, interpretation of TCD data in terms of absolute CBF should be made cautiously. However, TCD offers a continuous and non-invasive recording system with the ability to measure the trend in inadequate CBF reliably. Transcranial Doppler measurements have been used with success during carotid endarterectomy to detect perfusion changes following cross-clamping of the internal carotid. Padayachee *et al.*⁴⁴ have shown a significant decrease in MCA blood flow velocity during temporary occlusion of the internal carotid. Halsey *et al.*⁴⁵ showed that cortical CBF and CBFV correlated closely when CBF was low but not when CBF was high. Detection of emboli and inadequate blood flow during surgery are other indications. Albin *et al.*⁴⁶ detected high frequency signals that were related to air embolism. The TCD has allowed us to suggest that during hypothermic low-flow cardiopulmonary bypass CBF was not always assured.⁴⁷ Cerebral circulatory arrest related to decrease in intracranial compliance such as brain-dead subjects is associated with biphasic signal of low amplitude and a progressive reduction in the diastolic Doppler signal.⁴⁸

In summary, the results of this study indicate that in healthy children anaesthetized with 0.5 MAC or 1.0 MAC halothane or isoflurane, the responsiveness of the cerebral circulation to carbon dioxide measured by TCD on the MCA is preserved when the PETCO₂ is increased from 20 mmHg to 60 mmHg. Cerebrovascular reactivity to CO₂ may also be preserved with both volatile anaesthetic agents studied. However, the least intrinsic vasodilatory effect was observed with isoflurane. This may be of

possible benefit in neuroanaesthesia in the clinical concentrations studied compared with halothane. Further investigations are required to determine the possible effects of cerebrovascular reactivity to CO₂ at higher MAC multiples of isoflurane and halothane.

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