Cerebrovascular stability during isoflurane anaesthesia in children

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The aims of this study were firstly, to determine the effect of various concentrations of isoflurane on cerebrovascular circulation and secondly, to examine the time-response characteristics of the drug on cerebral blood flow velocity in anaesthetized children. Thirty-two ASA physical status I or II patients aged one to eight years and scheduled for urological surgery were studied. Anaesthesia was induced with thiopentone 5 mg · kg^{-1} and fentanyl 2 μg · kg^{-1}. Muscle relaxation was provided with vercuronium 0.1 mg · kg^{-1}. Tracheal intubation was performed in all cases. Anaesthesia was maintained with isoflurane in a mixture of air and oxygen to produce an inspired oxygen fraction (FIO_2) of 0.3. Ventilation was adjusted to maintain normocapnia. A caudal or lumbar epidural catheter was inserted before skin incision and a continuous bupivacaine, without epinephrine, infusion established. During the first part of this study, the initial isoflurane concentration for 24 patients was randomized and age-adjusted to 0.5 MAC, 1.0 MAC, or 1.5 MAC. After steady-state was reached, the subsequent isoflurane MAC concentration was randomized by either raising or lowering it from the initial concentration. In the second part of this study, the time-response effect of isoflurane was examined. Eight patients received 1.0 MAC isoflurane over 90 to 150 min. Temperature, heart rate, and systolic blood pressure were unchanged throughout the study. Cerebral blood flow velocity (CBFV) and resistance index (RI+), a measure of cerebrovascular resistance, were measured in the M1 segment of the middle cerebral artery (MCA) with a 2 MHz transcranial Doppler monitor. The CBFV and RI+ did not change when the initial isoflurane MAC concentration of either 0.5, 1.0, or 1.5 MAC, was varied. Furthermore, there was no change in CBFV and RI+ when isoflurane was administered over time. This indicates that varying isoflurane MAC concentrations between 0.5 MAC and 1.5 MAC did not have any effect on cerebral circulation and that the administration of a constant concentration of isoflurane over time does not affect cerebral haemodynamic variables in anaesthetized healthy children.

La présente étude a pour but d'identifier l'effet de différentes concentrations d'isoflurane ainsi qu'examiner l'effet de la durée d'administration sur la circulation cérébrovasculaire de 32 enfants, âgés de un á huit ans, ASA I ou II, et anesthésie pour interventions urologiques. L'induction de l'anesthésie a été pratiquée à l'aide de thiopentone 5,0 mg · kg^{-1} et de fentanyl 2,0 μg · kg^{-1}. La relaxation musculaire était assurée à l'aide de vécuronium 0,1 mg · kg^{-1} et la trachée intubée. Le maintien de l'anesthésie a été assuré à l'aide d'isoflurane dans un mélange d'air et d'oxygène de façon à produire une fraction inspirée d'oxygène (FIO_2) de 0,3. La ventilation mécanique était ajustée pour maintenir la normocapnie. Un bloc caudal ou un bloc lombaire épidural continu était administré avant le début de la chirurgie. Durant la première partie de cette étude, la concentration initiale d'isoflurane de 24 patients était ajustée de façon aléatoire, à 0,5, 1,0 ou 1,5 MAC, au tenant compte de la correction pour l'âge. Après avoir atteint l'état d'équilibre, la concentration d'isoflurane suivante était administrée, au hasard, d'une façon croissante ou décroisante par rapport à la concentration initiale. Durant la deuxième partie, nous avons examiné l'effet du temps sur l'administration continue de 1,0 MAC d'isoflurane chez huit patients anesthésiés pour une durée de 90 à 150 minutes. La pression artérielle systolique, le rythme cardiaque et la température sont demeurés inchangés durant toute la période étudiée. La vélocité du débit sanguin cérébral (CBFV) ainsi que l'index de résistance cérébrovasculaire (RI+) de l'artère cérébrale moyenne (MCA) ont été mesurés avec l'aide d'un moniteur Doppler transcranien utilisant une fréquence de

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2 MHz. La CBFV et le RI+ n'ont pas changé lorsque la concentration initiale d'isoflurane (0,5, 1,0, ou 1,5 MAC), était augmentée ou diminuée pour compléter la boucle. De plus, nous n'avons pas observé de changement de la CBFV et du RI+ lorsque l'isoflurane était administré pour une longue période de temps. Ces résultats démontrent que les différentes concentrations d'isoflurane n'affectent pas la circulation cérébrovasculaire et que la durée d'administration d'une concentration fixe d'isoflurane ne modifie pas certaines des variables hémodynamiques cérébrales lors de l'anesthésie chez des enfants sains.

Transcranial Doppler studies have been used for non-invasive diagnosis for 25 yrs. For more than a decade they have been used to estimate cerebral blood flow (CBF) in infants and children with open fontanelles.[1] In 1982, Aaslid *et al.* described the use of a 1–2 MHz doppler which could measure CBF in adults non-invasively.[2] These modifications have enabled reliable measurements of MCA flow velocity through the temporal bone in anaesthetized children.[3]

Halothane, a commonly used inhalational agent in paediatric neuroanaesthesia was shown by Lazzell *et al.* to cause an increase in cerebral blood flow velocity (CBFV) as the inspired concentration was increased.[4] This increase in CBFV was thought to be due to a simultaneous decrease in cerebrovascular resistance suggesting an abolition of cerebral autoregulation. The same investigators have shown that halothane exhibits a 30 to 45 min delay in return of CBFV to baseline values when the halothane concentration was decreased from 1.5 MAC to 0.2 MAC; this has been termed an hysteresis phenomenon.[5]

Isoflurane is now considered the inhalational agent of choice in neuroanaesthesia.[6] It causes less cerebral vasodilatation and brain surface protrusion than halothane or ethrane at equipotent concentrations but controversy exists regarding its effect on CBF at different concentrations.[7–8] An animal study by MacPherson *et al.* demonstrated that 1 MAC isoflurane did not change CBF whereas 2 MAC isoflurane caused substantial hyperaemia.[9] Vanaken *et al.* reported that cerebral blood flow changed passively with blood pressure at an isoflurane concentration greater than 1 MAC.[10] Gelman *et al.* using a dog model showed that 1 MAC and 2 MAC isoflurane caused vasodilatation of the cerebral vasculature to a greater degree than halothane.[11] Results of adult human studies in which isoflurane concentrations up to 1.5 MAC were used showed that CBF did not increase.[8] The effects of isoflurane on the CBFV in healthy children have not been reported previously.

Further controversy exists regarding the effect of isoflurane on CBF over time. Turner *et al.* demonstrated that it produced cerebral vasodilatation in dogs but that this effect diminished after two hours.[12] MacPherson *et al.* showed that 1.0 MAC isoflurane anaesthesia in normocapnic dogs caused a decrease in CBF over time.[13] However, a more recent study by Roald *et al.* showed that, in dogs, there was no change in CBF during three to four hours of steady-state 1% isoflurane anaesthesia.[14] The effect of prolonged isoflurane administration on CBF in human remains unknown.

This study was designed to determine: (1) the cerebrovascular response of increasing and decreasing the concentration of isoflurane between 0.5 to 1.5 MAC, and (2) to examine the time-response effect of isoflurane on CBFV and RI+ in healthy children.

Methods

Practical Procedure

Following approval from the Human Subjects Review Committee, informed written consent was obtained from the parents of 32 ASA physical status I or II children scheduled for elective urological surgery. All children were fasting and unpremedicated. Patients with cardiac or neurological disease and patients with a contraindication to regional anaesthesia were excluded. All patients were supine and horizontal throughout the study.

Patients were monitored in an appropriate manner for the induction of anaesthesia. Anaesthesia was induced with intravenous thiopentone 5 $mg \cdot kg^{-1}$, and fentanyl 2 $\mu g \cdot kg^{-1}$ followed by vecuronium 0.1 $mg \cdot kg^{-1}$ to facilitate tracheal intubation. The lungs were ventilated with air/O_2 by intermittent positive pressure at peak inspiratory pressures of 20–25 cm H_2O and an end-expiratory pressure of zero. Ventilation was adjusted to achieve normocapnia. Fresh gas flow was maintained at a constant rate throughout the study to avoid changes in intrathoracic pressure. Anaesthesia was maintained with isoflurane in a mixture of air and oxygen to produce an FIO_2 of 0.3. Muscle relaxation was maintained with vecuronium 0.05 $mg \cdot kg^{-1}$. A continuous caudal or lumbar epidural block using 0.25% bupivacaine without epinephrine was administered to all patients before incision. Normothermia was maintained using a Humid-Vent 1 (Gibeck-Dryden Corporation, Indianapolis, Indiana, USA)[15–16] and a warming blanket. Lactated Ringer's solution (5 $ml \cdot kg^{-1}$) was administered over the initial 15 min to replace the fluid deficit with a further 2 $ml \cdot kg^{-1} \cdot hr^{-1}$ allowed for maintenance. Additional fluid was given as needed to replace surgical losses.

Experimental protocol

Part I: In the first part of the study, 24 children were divided into three groups according to their initial isoflurane concentration. Each group received, initially, a

TABLE Data summary

	Isoflurane MAC							
Variables	*0.5[a]*	*0.5[b]*	*1.0[a]*	*1.0[b]*	*1.5[a]*	*1.5[b]*	*P[a]*	*P[b]*
HR (beats · min^{-1})	101 ± 20	103 ± 22	100 ± 24	100 ± 21	104 ± 23	103 ± 21	ns	ns
SABP (mmHg)	89 ± 11	91 ± 11	88 ± 10	89 ± 12	88 ± 7	93 ± 10	ns	ns
$PETCO_2$ (mmHg)	37 ± 3	39 ± 2	38 ± 2	37 ± 2	38 ± 3	37 ± 2	ns	ns
TEMP (°C)	37.0 ± 0.2	36.8 ± 0.1	36.9 ± 0.2	36.7 ± 0.2	36.9 ± 0.2	36.7 ± 0.2	ns	ns
AP (cm H_2O)	19 ± 3	20 ± 2	20 ± 2	20 ± 3	22 ± 2	21 ± 2	ns	ns
SaO_2 (%)	98 ± 2	99 ± 2	99 ± 2	99 ± 1	97 ± 2	98 ± 3	ns	ns
CBFV (cm · sec^{-1})	130.6 ± 25.7	132.6 ± 15.4	134.9 ± 25.3	133.5 ± 23.2	133.5 ± 28.8	134.9 ± 20.4	ns	ns
RI+	0.63 ± 0.07	0.60 ± 0.05	0.63 ± 0.06	0.61 ± 0.05	0.64 ± 0.05	0.63 ± 0.08	ns	ns

All values are mean (SD).

Abbreviations: HR, heart rate; SABP, systolic arterial blood pressure; $PETCO_2$, end-tidal CO_2; TEMP, temperature; AP, airway pressure; SaO_2, arterial oxygen saturation; CBFV, cerebral blood flow velocity; RI+, cerebrovascular resistance.

MAC^a values represent the initial minimum alveolar concentration from which isoflurane was subsequently either raised or lowered.

MAC^b values represent the final concentration.

[a]P values are obtained by paired t test comparing the initial and final concentration.

[b]P values are obtained by repeated-measures of variance and Student-Newman-Keuls for multiple comparisons within all isoflurane MACs.

randomized end-tidal concentration of isoflurane of either 0.5 MAC, 1.0 MAC or 1.5 MAC. After three measurements of CBFV and RI+ were obtained at the initial MAC, the patients then received the subsequent isoflurane concentrations which were either raised or lowered in random manner after which the initial concentration was resumed. Transcranial Doppler measurements were recorded for each isoflurane MAC after allowing 15 min to reach steady-state. Three visual displays to systolic and diastolic flow velocities (CBFV) and RI+ in the MCA were obtained at one minute intervals during periods of haemodynamic stability at each isoflurane MAC concentration value.

Part II: In the second part of the study, the time-response of isoflurane on CBFV and RI+ was measured in eight children. All patients received a steady-state 1.0 MAC isoflurane anaesthesia over a period of 90–180 min. Three measurements of CBFV and RI+ were recorded every 15 min.

Systolic arterial blood pressure, heart rate, arterial oxygen saturation, and inspired O_2 fractions were recorded simultaneously with the measurements of CBFV and RI+ throughout both segments of the study period. The end-tidal concentrations of isoflurane and CO_2 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).[17] The gas monitor was calibrated using a reference gas mixture before each use. The CBFV and RI+ were obtained from the continuous recording of the M1 segment of the middle cerebral artery using a transcranial Doppler sonography monitor (Transpect TCD Medasonics, Fremont, CA).[18]

Statistical analysis

The mean ± standard deviation (SD) for age, weight, systolic arterial blood pressure, heart rate, temperature, arterial O_2 saturation, and end-tidal CO_2 was determined. The analysis of each TCD file was done by an investigator (BB) unaware of the isoflurane concentration and the sequences at which each file were recorded. Based on a previous investigation,[19–21] a sample size of eight patients per initial isoflurane MAC concentration was determined by power analysis assuming a = 0.05, b = 0.2, and a difference in CBF between 0.5 MAC and 1.5 MAC of 30%. Paired t test was used to compare the initial and final isoflurane concentrations. Repeated-measures analysis of variance and the Student-Newman-Keuls test for multiple comparisons were used to determine statistical significance difference at each isoflurane MAC concentration for CBFV, RI+, HR, systolic arterial blood pressure, temperature, arterial O_2 saturation, and end-tidal CO_2. A $P < 0.05$ was accepted to express statistical significance.

Results

Part I: The mean ± SD age and weight of the 24 children were 46.3±27.3 months and 18.5±4.8 kg, respectively. Heart rate, systolic arterial blood pressure, arterial oxygen saturation, temperature and end-tidal CO_2 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, at 0.5 MAC, 1.0 MAC, and 1.5 MAC isoflurane. The CBFV and RI+ did not change when the initial isoflurane MAC concentration of either 0.5, 1.0, or 1.5 MAC was varied (Figure 1).

Part II: The mean ± SD age and weight of the eight children were 40.2±31.5 mo and 15.5±6.2 kg, respective-

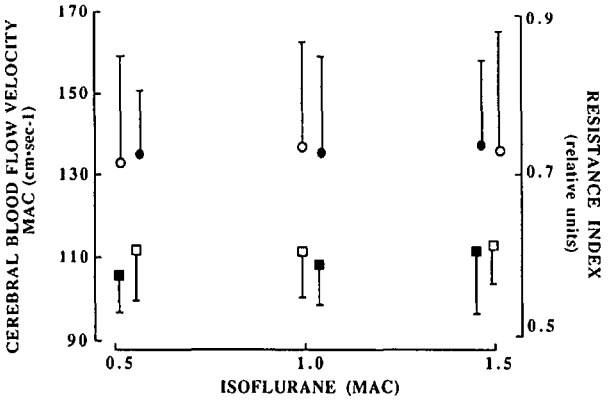

FIGURE 1 Cerebral blood flow velocity and cerebrovascular resistance at three MAC values. Cerebral blood flow velocity at (0.5–1.0–1.5 MAC) (○) and (1.5–1.0–0.5 MAC) (●) isoflurane was measured. The resistance index at (0.5–1.0–1.5 MAC) (□) and (1.5–1.0–0.5 MAC) (■) isoflurane was measured.

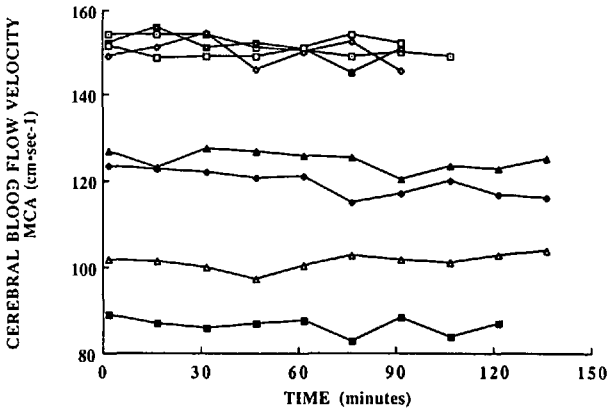

FIGURE 2 Cerebral blood flow velocity measured at 1.0 MAC isoflurane for 90 to 150 min in eight patients.

ly. All eight patients were given a steady-state 1.0 MAC isoflurane for 90 to 150 min and there was no change in CBFV over time (Figure 2). There were no complications from the use of the TCD in this study.

Discussion

The results of this study demonstrate that varying the isoflurane minimum alveolar concentration did not produce any effect on CBFV and RI+ in healthy anaesthetized children. Using the same methodology, Lazzell *et al.* showed that CBFV increased when the halothane concentration was increased between 0.5 MAC and 1.5 MAC.[4] In addition, it was observed that halothane caused a 30 to 45 min delay in the return of CBFV to the baseline value when the halothane concentration was decreased from 1.5 MAC to 0.2 MAC.[5]

In this study it was not possible to show a change in CBFV and RI+ at either 0.5, 1.0, or 1.5 MAC isoflurane. Thus, isoflurane did not exhibit the hysteresis phenomenon of CBFV and RI+ previously described using halothane in similar experimental conditions.[5]

The results of this study are in agreement with the conclusions of Eintrei *et al.* who measured CBF after applying small doses of ^{133}xenon on the exposed cortex and showed that there was no dose-dependent relationship in adult humans anaesthetized with isoflurane up to 1.5 MAC.[8] Algostsson *et al.* studied the effects of isoflurane on human cerebral blood flow and reported that isoflurane did not change CBF whereas halothane caused an increase of 36%.[22] Madsen *et al.* reported the absence of any changes in CBF in adult humans undergoing craniotomy for supratentorial cerebral tumour.[23] Todd *et al.* using a cat model reported that at three concentrations of 0.5, 1.0, and 1.5 MAC, isoflurane in the presence of N_2O had no effect on CBF and produced smaller decreases in cerebrovascular resistance than halothane.[24] However, MacPherson *et al.* using a dog model showed that increasing isoflurane concentration produced a non-autoregulated cerebral vascular bed.[13] Cucchiara *et al.* reported that canine cerebral blood flow increased by 33% and 63% at 1.4% and 2.4% concentrations, respectively.[20] They demonstrated that this effect was due to a decrease in cerebrovascular resistance and suggested that isoflurane was similar to halothane. Another explanation might be that the cerebral vasodilatation generated by isoflurane is counteracted by the decrease in mean arterial pressure. However, in the present investigation none of the children experienced any changes in MAP with the increase in isoflurane concentration. Furthermore, the absence of any change in cerbrovascular resistance suggests that isoflurane did not dilate the cerebral vessel studied.

In order to examine the contribution of time on the effect of isoflurane on the CBFV and RI+, we observed 1.0 MAC isoflurane anaesthesia over time in eight patients. We found that 1.0 MAC isoflurane administered for 90 to 150 min did not affect CBFV or RI+. These findings are consistent with those of Roald *et al.* who showed, using a very complex model, that 1% isoflurane had no effect on CBF during three to four hours of isoflurane anaesthesia.[14] However, Turner *et al.* reported in a dog model that CBF measured with 15 μm microspheres two hours after the induction isoflurane-nitrous oxide anaesthesia was significantly increased in all regions of the brain.[12] McPherson *et al.* showed that normocapnic CBF decreased over time with 1.4% isoflurane.[13]

In this study there are some methodological considerations that merit comment. The fact that isoflurane did not cause measurable change in the CBFV does not exclude

the possibility of a specific cerebral vasodilator property or an inability of our technology to detect such a change. Manohar *et al.* administered isoflurane to swine and found that 1.0 MAC isoflurane increased brain stem and cerebellar blood flow without increasing hemispheric CBF.[26] However, they observed that 1.5 MAC isoflurane increased hemispheric flow. In this study the Doppler monitor was used to measure flow velocity in a single vessel, the middle cerebral artery (MCA). The MCA is the largest branch of the basal cerebral artery providing some 70% of total blood flow of the ipsilateral hemisphere.[27] It is likely that any modification in cerebral blood flow velocity generated by isoflurane would be detectable from this important basal cerebral vessel.

With regard to the specificity of the transcranial Doppler, there are several assumptions underlying the relationship between CBFV and cerebral blood flow that have been discussed in previous publications.[18] Other potential considerations in the measurement of CBFV are errors based on the physics of ultrasound waves and Doppler instruments. The maximum error may be attributed to changes related to the angle of insonation and the Doppler resolution. Studies performed on cadavers showed that the M1 segment of the MCA can be insonated through the temporal windows with an angle of less than 20 degrees.[28] Because Doppler shift is proportional to the cosine of the angle and the CBFV is calculated from the shift in the ultrasound velocity, the maximum error generated by this variation is 7%. The individual variability as measured by the coefficient of variation was 4% which was less than the error due to the angle of insonation suggesting that we were within the limit for every patient. It may be that the resolution of the Doppler monitor is not good enough to identify small changes in CBFV. The Doppler resolution is determined by the frequency of the transducer (carrier frequency) and the angle at which the Doppler beam is used. The transpect TCD high-pass filters are active between 100 and 150 Hz which, accompanied with minimal angle of insonation, translates to a minimal display velocity of 3 $cm \cdot sec^{-1}$. If any changes of this magnitude in CBFV had been observed among the three different minimum alveolar concentrations studied, it only helps to confirm the lack of effect of isoflurane on cerebral vasculature.

The time constant for the equilibration of brain grey matter and blood for isoflurane is three minutes.[29] We waited 15 min to achieve steady-state conditions with isoflurane within the brain. If these equilibrium periods had been inadequate, then CBFV would have changed between the first and third measurements in any particular patient for any set of conditions. Our data showed no consistent changes between the first and third measurements. The calculated coefficients of variation were 5.3% for the CBFV and 6.6% for RI+ measurements. Thus, the equilibrium periods used for isoflurane produced steady-state conditions within the basal cerebral arteries of the brain.

We estimated the arterial PCO_2 by measuring the $PETCO_2$ at the distal tip of the endotracheal tube. Previous studies have shown that both single-breath and continuous distal $PETCO_2$ closely approximates $PaCO_2$ in healthy infants and children.[17,30]

Intrathoracic pressure affects cerebral perfusion pressure by its indirect effect on cerebral venous pressure. We maintained a constant mean intrathoracic pressure during each study to preclude the effect of changes in ventilation on CBFV. The $PETCO_2$ was adjusted to achieve normocapnia after which the ventilator settings were not modified. Thus, the observed changes in CBFV could not be attributed to changes in intrathoracic pressure.

Individual variability could introduce error into our measurements. Age is a major determinant of the CBFV.[31] There is a linear increase in CBFV from birth to the age of two months; thereafter it increases more slowly to reach its peak value at six years of age and then decreases slowly to 70% of this peak at age 16. The CBFV decreases an additional 20% between 20 and 60 yr.[32,33] In this study, the patient age range was one to eight years which suggest that the large standard deviations are probably related to these physiological variations rather than the pharmacological effect of isoflurane. All patients had similar haemoglobin concentrations (12–14 $mg \cdot dl^{-1}$), metabolic demands (normothermia was maintained), and haemodynamic profiles (no change in blood pressure or heart rate at any time), thereby reducing the contributions of these factors on the variability observed.

We concluded that cerebral blood flow velocity and cerebrovascular resistance are maintained at a constant levels during isoflurane anaesthesia between 0.5 MAC and 1.5 MAC. In addition, the effect of the prolonged administration of 1.0 MAC isoflurane failed to show a time-response effect on cerebral circulation. Can these observations be applied to a patient with increased intracranial pressure? Lazzell *et al.* using the same anaesthetic technique, showed that in children with acutely elevated intracranial pressure changes in CBFV and RI+ were related to surgical decompression and not to isoflurane.[34] The degree of impairment observed was dependent on the initial intracranial pressure and its position on the intracranial elastance curve. The clinical importance of these observations in patients with increased intracranial pressure would suggest that cerebrovascular stability conferred by isoflurane between 0.5 MAC and 1.0 MAC may make it the drug of choice in these circumstances. Moreover, the lack of a dose-dependent relationship over time of 1.0 MAC isoflurane on the cerebral vasculature of

anaesthetized healthy children adds further to its suitability in neurosurgical patients. The speculative nature of this conclusion needs to be confirmed by further investigations where the effects of higher MAC multiples of isoflurane on cerebrovascular circulation and the effect of isoflurane on patients with reduction in cerebral compliance have yet to be investigated.

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