Cerebrovascular carbon dioxide reactivity in children anaesthetized with sevoflurane

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Background. To determine the effects of sevoflurane on cerebrovascular carbon dioxide reactivity (CCO2R), middle cerebral artery blood flow velocity (CBFV) was measured at different levels of PECO2 by transcranial Doppler sonography in 16 ASA I or II children, aged 18 months to 7 yr undergoing elective urological surgery.

Methods. Anaesthesia comprised 1.0 MAC sevoflurane and air in 30% oxygen delivered through an Ayre’s T piece by intermittent positive-pressure ventilation, and a caudal epidural block with 0.25% bupivacaine 1.0 ml kg⁻¹ without epinephrine. PECO2 was randomly adjusted to 25, 35, 45 and 55 mm Hg (3.3, 4.6, 5.9 and 7.2 kPa) with an exogenous source of CO₂, while maintaining ventilation variables constant.

Results. CBFV increased as PECO2 increased from 25 to 35, and to 45 mm Hg (P<0.001), but did not increase significantly with an increase in PECO2 from 45 to 55 mm Hg. Mean heart rate and arterial pressure remained constant.

Conclusion. CCO2R is preserved in healthy children anaesthetized with 1.0 MAC sevoflurane.

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convective air warmer under the surgical drapes. The patients were kept supine and horizontal throughout the study period. Following stabilization of maintenance anaesthesia, ventilation was adjusted to achieve a $P_{\text{ET}}\text{CO}_2$ of 25 mm Hg (3.3 kPa). Thereafter, fresh gas flow and ventilation variables were maintained constant. The $P_{\text{ET}}\text{CO}_2$ was randomly adjusted to 25, 35, 45 and 55 mm Hg (3.3, 4.6, 5.9 and 7.2 kPa) by the addition of CO₂ to the Ayre’s T piece from an exogenous source. The first and subsequent levels of $P_{\text{ET}}\text{CO}_2$ were determined randomly until the last one was reached. The randomization was undertaken using computer-generated random number tables. Measurements were started after a 3 min stabilization period following changes in $P_{\text{ET}}\text{CO}_2$.

CBFV was measured by transcranial Doppler (TCD) sonography (Neuroguard, Medasonics, CA). The M1 segment of the middle cerebral artery was insonated through the temporal window with a range-gated 2 MHz Doppler probe, which was fixed to the subject’s head using a special device to maintain a constant angle of insonation throughout the study period. Additional technical specification of the TCD probe and details of Doppler analysis have been described. Three measurements were made, at 1-min intervals, at each $P_{\text{ET}}\text{CO}_2$. The TCD data were recorded on a computer and subsequently analysed by one investigator who was unaware of the sequence of changes in $P_{\text{ET}}\text{CO}_2$. Mean CBFV was calculated as the time-averaged area under the curve of 10 consecutive Doppler tracings. Non-invasive arterial pressure, heart rate, end-tidal sevoflurane concentration, airway pressure, ventilatory frequency, $\text{SaO}_2$, and rectal temperature were recorded at each level of $P_{\text{ET}}\text{CO}_2$ (SC 9000XL; Siemens, Sweden). The CO₂ was sampled from the tracheal tube using a 19G catheter (Intracath; Becton Dickinson, CA) and the CO₂ analyser (Capnomac Ultima, Datex, USA) was calibrated with a reference gas mixture before each study patient.

### Statistical analysis

All data with parametric values are expressed as mean (SD). The number of patients needed to demonstrate a direct effect on CBFV during changes in $P_{\text{ET}}\text{CO}_2$ was calculated with the assumption that a 20% change would be clinically relevant. Based on previous data demonstrating a CBFV of 78 (SD 21) cm s⁻¹ with 1.0 MAC sevoflurane at 40 mm Hg (5.3 kPa) $P_{\text{ET}}\text{CO}_2$ in a comparable group of children, and a statistical power of 0.8, an $\alpha$ of 0.05 and $\beta$ of 0.2, a total of seven patients was suggested. Sixteen patients were studied to account for methodological difficulties that could have led to exclusion from the study. The relationship between $P_{\text{ET}}\text{CO}_2$ and CBFV was obtained by non-linear regression analysis and the correlation coefficient ($r$) was calculated. Parametric data were analysed by repeated-measures ANOVA and the Student–Newman–Keuls test for multiple comparisons where appropriate. A value of $P<0.05$ was accepted as significant. The degree of relative dispersion was measured using the coefficient of variation for the CBFV data, which helps to determine the extent of the measurement effect on the results.

### Results

The mean age of the 16 children was 4 (SD 1.6) (range 1.5–7) yr and the mean weight was 16.8 (SD 4.6) (range 8.4–26) kg. Heart rate and mean arterial pressure remained constant throughout the study period (Table 1). The caudal block was successful in all cases. The TCD measurements were completed in all children, at all levels of $P_{\text{ET}}\text{CO}_2$, and there were no complications observed with the use of TCD sonography in this study. The CBFV increased markedly as $P_{\text{ET}}\text{CO}_2$ was changed from 25 to 35 mm Hg (3.3 to 4.6 kPa) ($P<0.001$) and from 35 to 45 mm Hg (4.6 to 5.9 kPa) ($P<0.001$). However, CBFV did not increase significantly when the $P_{\text{ET}}\text{CO}_2$ was raised from 45 to 55 mm Hg (5.9 to 7.2 kPa) (Table 1). The correlation coefficient ($r$) between CBFV and $P_{\text{ET}}\text{CO}_2$ was 0.89 (Fig. 1). The CCO₂R expressed as the percentage change in mean CBFV for a 1 mm Hg change in $P_{\text{ET}}\text{CO}_2$ was 8.6% as $P_{\text{ET}}\text{CO}_2$ increased from 25 to 35 mm Hg, and 5.1% from 35 to 45 mm Hg. It was only 0.8% as $P_{\text{ET}}\text{CO}_2$ increased from 45 to 55 mm Hg (Table 2). The degree of relative dispersion measured using the coefficient of variation for the CBFV data was 8.9%.

### Discussion

The results of this study demonstrate that CCO₂R is preserved in healthy children anaesthetized with 1.0 MAC sevoflurane. Similar findings have been reported in adults anaesthetized with sevoflurane. CO₂ exerts a rapid and considerable influence on the cerebral circulation by dilating the cerebral arterioles and increasing cerebral blood flow. It has been postulated that this effect occurs...
as a result of rapid diffusion of CO₂ from the arterial blood into arteriolar smooth muscle causing a change in extracellular pH. The observed CCO₂R of 8.6% with sevoflurane in the present study is considerably greater than the 2.6% with 1.0 MAC isoflurane and 1.4% with 1.0 MAC halothane reported by Leon and Bissonnette in a comparable group of children using a similar protocol. It is also greater than the 2.1% reported by Nishiyama and colleagues with 0.7 MAC sevoflurane in adults. Hence during sevoflurane anesthesia in children, small changes in \( P_{ECO_2} \) could have a clinically significant effect on cerebral blood flow and intracranial pressure. Furthermore, Nishiyama and colleagues reported that CCO₂R was greater for isoflurane than for sevoflurane in adults, but comparison of the data of the present study with that reported by Leon and Bissonnette suggests that the opposite may be true in children.

A plateau in CCO₂R between a \( P_{ECO_2} \) of 45 and 55 mm Hg was observed in this study, which was also observed by Leon and Bissonnette with isoflurane in adults, but has not been reported with any volatile agent in children. In children, unlike adults, cerebral vasodilatation seems maximal with 1.0 MAC sevoflurane above 45 mm Hg \( P_{ECO_2} \). Pilato and colleagues have also demonstrated this effect in a comparable group of children undergoing intravenous anaesthesia without a volatile agent. This may suggest that the observed effect is a characteristic of the cerebral vasculature in this age group and not an effect of the volatile agent. It has been demonstrated that acute hypercapnia can reduce the capacity for cerebral autoregulation, presumably with a loss of cerebrovascular vasodilatation in response to changes in perfusion pressure. This effect may therefore be occurring at or above the upper range of normal \( P_{ECO_2} \), in children anaesthetized with 1.0 MAC sevoflurane.

The stability of the heart rate and mean arterial pressure throughout the study period suggests that the observed changes in CBFV were not a result of cardiovascular alteration nor were they likely to have been caused by surgical stimulation, which seems to have been successfully obtunded by the caudal epidural block. Other determinants of CBFV were also controlled. Body temperature and depth of anaesthesia were maintained constant. Intrathoracic pressure was maintained constant by keeping the fresh gas flow rate and ventilation variables at the settings required to achieve the initial \( P_{ECO_2} \) of 25 mm Hg throughout the study period. The \( P_{ECO_2} \) was changed by addition of CO₂ to the T piece from an exogenous source, preventing any alteration in intrathoracic pressure and cerebral venous return.

Normal CBFV changes with age, increasing rapidly from birth to approximately 18 months, followed by a relatively minimal increase up to a peak at 7 yr and thereafter declining with increasing age. Thus CBFV in our study population, aged 18 months to 7 yr, should be relatively unaffected by age. The Doppler probe was fixed to the subject’s head, using a custom-designed frame, to maintain a constant angle of insonation (i.e., the angle at which the Doppler beam impacts on the artery) throughout the study period and hence avoid interpatient errors in the calculation of CBFV. Interpatient variability in the calculation of CBFV can result from different probe positions causing changes in the angle of insonation, which can range from 0 to 30 degrees for the middle cerebral artery. These variations could result in a maximum measurement error of 15%. The calculated coefficient of variation for both intra- and interpatient measurements demonstrated a relative dispersion within acceptable experimental limits. It has been shown that cerebral blood flow responds rapidly to

Table 2: Variations in cerebrovascular CO₂ reactivity (CCO₂R) expressed as the percentage change in mean CBFV for a 1 mm Hg change in \( P_{ECO_2} \), with increasing \( P_{ECO_2} \) in children anaesthetized with 1.0 MAC sevoflurane. Results are expressed as mean (SD).

<table>
<thead>
<tr>
<th>( \Delta P_{ECO_2}(\text{mm Hg}) )</th>
<th>25–35</th>
<th>35–45</th>
<th>45–55</th>
</tr>
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<tbody>
<tr>
<td>( P_{ECO_2}(\text{mm Hg}) )</td>
<td>3.3–4.6</td>
<td>4.6–5.9</td>
<td>5.9–7.2</td>
</tr>
<tr>
<td>CCO₂R (% mm Hg)</td>
<td>8.6 (2.9)</td>
<td>5.1 (3.2)</td>
<td>0.8 (0.5)</td>
</tr>
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changes in $P_{ACO_2}$ and reaches a plateau within 2 min.9 Three min was allowed after each change in $P_{ECO_2}$ to achieve steady-state conditions within the brain. There was no variability between the first and third measurements at each level of $P_{ECO_2}$, which allows us to assume that the steady-state conditions for CO2 were present within the basal arteries of the brain during the measurement periods. The $P_{ECO_2}$ was sampled from the connector of the tracheal tube to prevent any mixing effect from the fresh gas flow.15 Furthermore, it has been shown that $P_{ECO_2}$ closely approximates to $P_{ACO_2}$ in healthy children.16 17 Young and colleagues reported that the cerebral blood flow response to changes in CO2 tension in adults can be reliably estimated from measurement of $P_{ECO_2}$.18 Having accounted for all the confounding factors that could affect the CBFV and the possible measurement errors, one can conclude that the observed changes in CBFV are attributable to changes in $P_{ECO_2}$.

TCD sonography was used to measure the effect of changing $P_{ECO_2}$ on CBFV. It is a simple non-invasive and reproducible method of measuring CBFV. Relative changes in CBFV have been shown to correlate well with changes in cerebral blood flow measured by intravenous xenon13 3 clearance ($r=0.84$) and radioactive microspheres ($r=0.94$).19 20 In order for this to be true, the cross-sectional area of the M1 segment of the middle cerebral artery must not alter significantly with changes in arterial pressure, $P_{ACO_2}$ or the use of anaesthetic agents. This has been verified by direct measurement during craniotomy, and using both angiography and Doppler signal power analysis.21 23 Furthermore, Gillard et al. have demonstrated the reliability of TCD to insonate the M1 segment of the middle cerebral artery through the temporal window in the paediatric population.24 TCD sonography is now widely used as a surrogate measure of cerebral blood flow.25

Sevoflurane appears to demonstrate the properties of a suitable anaesthetic agent for adult neurosurgical procedures. It causes less intrinsic cerebral vasodilatation and preserves dynamic cerebral autoregulation in response to changes in mean arterial pressure.3 4 26 28 It does not seem to cause an epileptiform EEG or an increase in intracranial pressure during neurosurgery.29 30 The present study shows that, with respect to $CCO_2R$, sevoflurane could be a suitable agent for paediatric neurosurgical procedures. We have previously shown in children that CBFV is not affected by changes in sevoflurane concentration from 0.5 to 1.5 MAC.8 We have also reported that the effect on CBFV of adding nitrous oxide to sevoflurane is similar to adding it to isoflurane.31 Taking account of all of these findings, we can say that sevoflurane demonstrates some of the ideal properties of an anaesthetic agent for paediatric neurosurgical procedures. However, a direct clinical comparison of sevoflurane with other anaesthetic agents is necessary to decide which is the ideal agent for this indication.

References

20 Kochs E, Hoffman WE, Werner C, et al. Cerebral blood flow