Cerebrovascular reactivity to carbon dioxide is preserved during hypocapnia in children anesthetized with 1.0 MAC, but not with 1.5 MAC desflurane

[La réactivité cérébrovasculaire au gaz carbonique est conservée pendant l'hypocapnie chez des enfants anesthésiés avec 1,0 CAM, mais non avec 1,5 CAM, de desflurane]

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Purpose: Maintenance of cerebrovascular reactivity to CO_2 (CCO_2R) is important during neurosurgical anesthesia. This study was designed to determine the effect of different desflurane concentrations on CCO_2R in children.

Methods: Children undergoing urological surgery were enrolled. Anesthesia was induced with sevoflurane in air/oxygen. After intubation, sevoflurane was switched to desflurane. Analgesia was provided with an epidural neuraxial block. Mechanical ventilation was adjusted to an initial $EtCO_2$ of 30 mmHg. Exogenous CO_2 was used to achieve an $EtCO_2$ of 40 and 50 mmHg. Patients were randomized to the sequence of desflurane concentration (1.0 and 1.5 MAC) and the $EtCO_2$. Transcranial Doppler was used to measure middle cerebral artery blood flow velocity (Vmca). Five minutes were allowed to reach steady state after each change in $EtCO_2$ and 15 min after changing the desflurane concentration.

Results: Sixteen patients were studied. The mean age and weight were 3.5 ± 1.5 yr and 14.4 ± 3.1 kg, respectively. Mean arterial pressure remained stable throughout the study, while at an $EtCO_2$ of 50 mmHg, heart rate decreased at both desflurane concentrations ($P < 0.05$). At 1.0 MAC, Vmca increased from 30 to 40 mmHg ($P < 0.05$), but not from 40 to 50 mmHg $EtCO_2$. At 1.5 MAC, Vmca increased between 30 and 50 mmHg ($P < 0.05$).

Conclusion: CCO_2R is preserved during hypocapnia in children anesthetized with 1.0 MAC, but not with 1.5 MAC desflurane. The lack of further increase in Vmca at higher $EtCO_2$ concentrations implies that desflurane may cause significant cerebral vasodilatation in children. This may have important implications in children with reduced intracranial compliance.

Objectif : *Le maintien de la réactivité cérébrovasculaire au CO_2 ($RCCO_2$) est important pendant l'anesthésie neurochirurgicale. Nous voulions déterminer l'effet de différentes concentrations de desflurane sur la $RCCO_2$ chez des enfants.*

Méthode : *Les enfants choisis devaient subir une intervention urologique. L'anesthésie a été induite avec du sévoflurane dans un mélange d'air et d'oxygène. Après l'intubation, le sévoflurane a été remplacé par du desflurane. L'analgésie a été prodiguée par un bloc neuraxial péridural. La ventilation mécanique a été réglée selon un $EtCO_2$ initial de 30 mmHg. Du CO_2 exogène a permis d'obtenir un $EtCO_2$ de 40 et 50 mmHg. Les patients, répartis au hasard, ont reçu la séquence de desflurane (1,0 et 1,5 CAM) et de $EtCO_2$. La vitesse circulatoire de l'artère cérébrale moyenne (Vacm) a été mesuré par Doppler transcrânien. L'état d'équilibre a été atteint en 5 min après chaque changement de $EtCO_2$ et 15 min après la nouvelle concentration de desflurane.*

Résultats : *L'étude a porté sur 16 patients. L'âge et le poids moyens étaient de 3,5 ± 1,5 ans et 14,4 ± 3,1 kg. La tension artérielle a été stable tout au long de l'étude, tandis que pour un $EtCO_2$ de 50 mmHg, la fréquence cardiaque a diminué avec les deux concentrations de desflurane ($P < 0,05$). À 1,0 CAM, la Vacm a augmenté pour un $EtCO_2$ de 30 à 40 mmHg ($P < 0,05$), mais non de 40 à 50 mmHg. À 1,5 CAM, la Vacm s'est élevée entre 30 et 50 mmHg ($P < 0,05$).*

Conclusion : *La $RCCO_2$ est conservée pendant l'hypocapnie chez des enfants anesthésiés avec 1,0 CAM, mais non avec 1,5 CAM, de desflurane. L'absence d'une nouvelle augmentation de la Vacm pour des concentrations plus élevées de $EtCO_2$ sous-entend que le desflurane peut causer une vasodilatation cérébrale significative chez les enfants. Ce résultat peut avoir d'importantes implications chez les enfants qui présentent une compliance intracrânienne réduite.*

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CARBON dioxide has a rapid and important influence on the cerebral vasculature. Rapid diffusion of CO_2 from the arterial blood into the arteriolar smooth muscle cells generates a change in perivascular pH, which is thought to be responsible for the maintenance of cerebrovascular reactivity to CO_2 (CCO_2R).[1] At hypocapnia, this results in reduced cerebral blood flow and cerebral blood volume and may be used to control the intracranial pressure (ICP).

The favourable physico-chemical properties of desflurane (low blood-gas and tissue solubility) make it a potentially suitable anesthetic agent for neuroanesthesia, allowing for rapid emergence and postoperative neurological assessment. Studies in adults have reported that CCO_2R is preserved during desflurane anesthesia.[2–4] In children, the effects of desflurane on CCO_2R are not as well defined. In a study of ten children,[4] cerebral blood flow velocity (CBFV) was recorded during the first ten minutes of desflurane administration while the $EtCO_2$ was changed from 40 to 30 mmHg. Based on their observations, the authors suggested that CCO_2R is preserved during desflurane anesthesia. However, the lack of steady state conditions might have limited the identification of the cerebrovascular effects of desflurane on the CCO_2R.

This study was designed to determine the effects of two different desflurane concentrations on the CCO_2R in children at hypo-, normo- and hypercapnia.

Methods

After approval by the Institutional Research Ethics Board and written informed parental consent, 16 unpremedicated children aged two to six years, ASA I or II, undergoing elective urological surgery were enrolled. Children with a history of prematurity, cardiac, pulmonary, or neurological disease, or a contraindication to regional anesthesia were excluded from the study.

Anesthesia was induced by facemask with sevoflurane in oxygen. Standard monitoring included electrocardiogram, pulse oxymetry, non-invasive arterial blood pressure, and a nasopharyngeal temperature probe. A peripheral venous cannula was inserted and orotracheal intubation facilitated with rocuronium 1.0 $mg \cdot kg^{-1}$. Immediately after tracheal intubation, sevoflurane was discontinued and intermittent positive pressure ventilation (IPPV) with desflurane in air/oxygen (FIO_2 = 0.35) with a fresh-gas flow of 3 $L \cdot min^{-1}$ was initiated, using a circle system and an Air-Shields ventilator (Air-Shields Vickers®, Hatboro, USA). Peak inspiratory pressures were kept at 20 mmHg and the respiratory rate was adjusted to achieve an initial end-tidal CO_2 ($EtCO_2$) of 30 mmHg. No positive end- expiratory pressure was used at any time during the study period. Exogenous CO_2 was administered to achieve $EtCO_2$ levels of 40 and 50 mmHg. $EtCO_2$ was measured using a central venous catheter (Intracath 19 Gauge, 30.5 cm, Becton-Dickinson®, Sandy, USA) advanced to the distal tip of the endotracheal tube. The desflurane concentration, fraction of inspired oxygen concentration (F_iO_2) and $EtCO_2$ were continuously analyzed with a Capnomac Ultima monitor (Datex Instruments Corporation®, Helsinki, Finland). A caudal epidural block with 1.0 $mL \cdot kg^{-1}$ of plain bupivacaine 0.25% was performed for each patient. Surgery was allowed to commence 15 min after the caudal block had been performed and the block was assumed to be successful if upon skin incision the heart rate and mean arterial pressure did not increase more than 5% from baseline (immediately before skin incision). All children were kept supine and horizontal throughout the study period. Normothermia was maintained using a conductive water mattress (Gaymar® T/Pump, Gaymar Industries, New York, USA) and/or convective forced air-warming system (Bair Hugger®, Augustine Medical Inc., Eden Prairie, USA).

The transcranial Doppler (TCD) probe was placed over the right temporal window and adjusted to insonate the M1 segment of the middle cerebral artery (MCA) to measure systolic and mean cerebral blood flow velocity (Vmca). A pulse-gated TCD with a 2-MHz emitted ultrasonic frequency (Neuroguard, Medasonics®, Fremont, USA) was used and the Doppler shift data was processed and displayed by a real-time spectral analyzer. A custom made wheel was used to fix the TCD-probe to the patient's head to keep the angle of insonation constant.[5]

Patients were randomized to the order of desflurane concentration (1.0 and 1.5 age-adjusted MAC)[6] as well as to the sequence of the $EtCO_2$ concentration (30, 40 and 50 mmHg) using computer generated random number tables. Fifteen minutes were allowed to reach steady state after changing the desflurane concentration and five minutes after changing the $EtCO_2$ concentration. At each $EtCO_2$ level, three measurements were recorded at one- minute intervals. Vmca, heart rate (HR), mean arterial pressure (MAP), $EtCO_2$ and desflurane concentrations were simultaneously measured. After the desflurane concentration was changed, the same sequence of $EtCO_2$ concentrations was repeated.

Demographic and parametric data are expressed as mean ± SD. The number of patients needed to demonstrate a direct effect on CBFV was calculated with the assumption that a 20% change in Vmca would be clini-

cally relevant. Based on a statistical power of 0.8, an α_2 = 0.05 and a ß = 0.2, seven patients were suggested. A total of 16 patients were studied to account for methodological difficulties that could have led to exclusion from the study. Vmca, HR and MAP were analyzed with repeated measures ANOVA and Tukey-Kramer HC for multiple comparisons. The Vmca data files were stored on a computer (Apple Macintosh®, Cupertino, USA) and later analyzed by an investigator unaware of the randomization and the hemodynamic response. A $P < 0.05$ was accepted for statistical significance.

Results

Sixteen patients were studied, with a mean age and weight of 3.5 ± 1.5 yr and 14.4 ± 3.1 kg, respectively. The caudal block was successful in all cases and TCD measurements were completed in all children. MAP remained stable throughout the study period. At both desflurane concentrations, the increase in $EtCO_2$ from 30 to 40 mmHg did not affect the HR, however it decreased significantly at 50 mmHg ($P < 0.05$).

At 1.0 age-adjusted MAC desflurane, increasing $EtCO_2$ from 30 to 40 mmHg resulted in an increase in Vmca from 58 ± 14 cm·sec^{-1} to 72 ± 16 cm·sec^{-1} ($P < 0.05$), however, it did not increase further between 40 and 50 mmHg (72 ± 16 cm·sec^{-1} to 73 ± 17 cm·sec^{-1}; Figure). When $EtCO_2$ was increased from 30 to 40 mmHg at 1.5 age-adjusted MAC desflurane, Vmca did not change significantly (from 51 ± 16 cm·sec^{-1} to 59 ± 11 cm·sec^{-1}), but at 50 mmHg $EtCO_2$, Vmca increased significantly (to 66 ± 13 cm·sec^{-1}) when compared to 30 mmHg ($P < 0.05$; Figure).

At 1.0 MAC desflurane, the CCO_2R expressed as the percent change in mean CBFV per 1 mmHg change in $EtCO_2$ was 2.45 between 30 and 40 mmHg and 0.14 between 40 and 50 mmHg. At 1.5 MAC, the corresponding values were 1.56 and 1.25, respectively.

There were no complications as a result of this study.

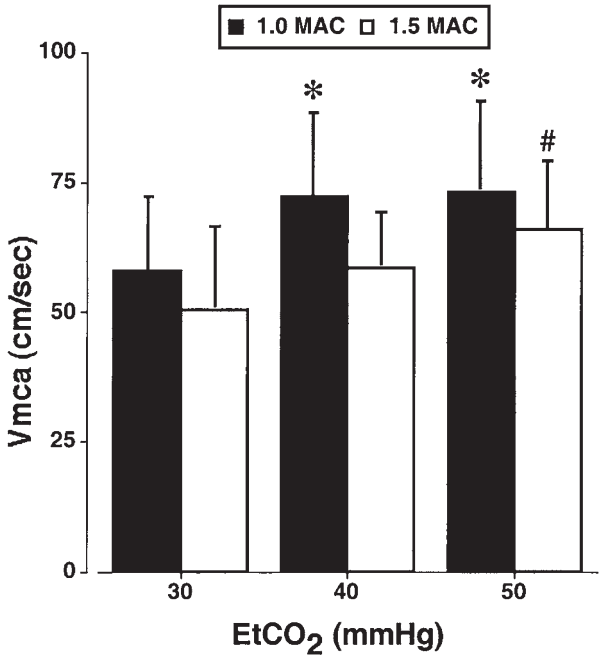

FIGURE Cerebral blood flow velocity in the middle cerebral artery (Vmca) at different desflurane and $EtCO_2$ concentrations. * denotes a significant increase in Vmca when compared to baseline (30 mmHg $EtCO_2$; $P < 0.05$); # indicates a significant change when compared to baseline (30 mmHg $EtCO_2$; $P < 0.05$).

Discussion

This study suggests that cerebrovascular reactivity to CO_2 is preserved at hypocapnia in children anesthetized with 1.0 MAC desflurane, but is reduced at 1.5 MAC. The expected increase in Vmca associated with hypercapnia seems attenuated, suggesting that desflurane may maximally dilate the cerebral vasculature and that the addition of CO_2 does not contribute to further increases in Vmca.

A previous study in children comparing three different desflurane concentrations showed a significantly increased Vmca at 1.0 MAC when compared to 0.5 MAC desflurane, without any further increases at 1.5 MAC.[7] These observations support the concept that cerebral vasodilatation in children is already maximal during anesthesia with 1.0 MAC desflurane at normocapnia. These findings are not supported by a previous study in adults reporting that desflurane caused further cerebral vasodilatation at 1.5 MAC when compared to 0.5 MAC.[8] However, propofol was used to induce cerebral isoelectricity before the addition of desflurane. It is therefore very likely that the cerebral vessels were already vasoconstricted due to propofol and that the net effect of desflurane resulted in cerebral vasodilatation.

In the present study, the small differences in CBFV observed between 1.0 and 1.5 MAC desflurane at all three $EtCO_2$ concentrations could be explained by the "dual action hypothesis".[9,10] The authors of these studies have suggested that desflurane causes a direct cerebral arterial vasodilatation independent of cerebral metabolism, even though desflurane keeps the flow-metabolism coupling intact. The reduction in cerebral metabolic rate of oxygen ($CMRO_2$) associated with deeper anesthesia means that desflurane also causes

cerebral vasoconstriction. Therefore, what is measured clinically is the result of a subtle balance between these two antagonizing effects. It is possible that at the higher desflurane concentration the cerebral vasconstriction as a result of the decreased $CMRO_2$ becomes more prominent, as suggested by Mielck *et al.*[3] In that study, CCO_2R was preserved at 1.0 MAC desflurane.

A recent study with 1.0 age-adjusted MAC sevoflurane in children reported CCO_2R values of 8.6%/mmHg from 25 to 35 mmHg and 5.1%/mmHg from 35 to 45 mmHg.[11] These authors also demonstrated a loss of CCO_2R at hypercapnia. Although the $EtCO_2$ intervals were slightly different in that study, these values are considerably greater and reflect the well preserved CCO_2R during sevoflurane anesthesia. This implies that changes in P_aCO_2 result in more pronounced changes in cerebral vasculature in children anesthetized with sevoflurane than with other inhalational anesthetics. The CCO_2R for isoflurane and halothane in the range of 20 to 40 mmHg were reported as 2.6 and 1.4%/mmHg, respectively.[12]

Desflurane and isoflurane showed similar effects with respect to CCO_2R in adults when CBF and CCO_2R were measured by *iv* ^{133}Xenon.[2] Although the authors only examined the CCO_2R at 25 and 35 mmHg P_aCO_2, they reported that CCO_2R at 1.0 MAC desflurane and isoflurane is maintained at about 1.3 to 1.6 %/mmHg. Mielck *et al.*[3] used a modified Kety-Schmidt saturation technique with argon as inert tracer gas to measure CBF in adults and suggested that CCO_2R is preserved at 1.0 MAC desflurane between an $EtCO_2$ of 30 and 50 mmHg.

In a recent pediatric study, Brenet *et al.*[4] concluded from ten children that CCO_2R remains intact at 1.0 age- adjusted MAC desflurane. However, the children received propofol, atropine, fentanyl, and atracurium for induction of anesthesia and tracheal intubation. Within the first minute following tracheal intubation and administration of desflurane, baseline CBFV measurements were recorded and subsequent recordings were obtained every minute for the next ten minutes. One may speculate that a state of hyperdynamic circulation was still present, that the cerebral vasoconstrictive effect of propofol was most likely still in effect and that the brain partial pressure of desflurane had reached a steady state only at the end of the study period. It has also been demonstrated that rapid increases in desflurane concentration stimulate the sympathetic nervous system[13–15] and a period of up to nine minutes is necessary to abate this effect.[16] Although fentanyl has been shown to attenuate the cardiovascular stimulation triggered by desflurane in adults,[17] the situation remains unclear in children. To prevent the addition of confounding factors, neither opioids nor atropine were used in the present study.

All patients received sevoflurane for induction of anesthesia. With a brain/blood partition coefficient of 1.7,[18] the calculated time constant for equilibration in the grey matter of the brain is approximately 3.4 min, thus the time to 98% equilibration of the anesthetic partial pressure (i.e., four time constants) equals 13.6 min. After discontinuation of sevoflurane, we allowed 15 min for elimination of sevoflurane.

The equilibration time constant for desflurane within the brain has been calculated as about 2.6 min.[18] Fifteen minutes were allowed between changes in the desflurane concentration and before recording the first CBFV measurement in order for steady state to be reached. The time constant for the acute effects of carbon dioxide on cerebral arteries is approximately one minute.[19] In the present study five minutes were allowed to reach equilibration within the brain. Measurements of $EtCO_2$ were used to estimate P_aCO_2. In healthy children, it has been shown that $EtCO_2$ closely approximates P_aCO_2.[20] The accuracy of the $EtCO_2$ measurement was increased using a central venous catheter advanced inside of the endotracheal tube (ETT) adjusted to allow sampling from the distal end of the ETT.[21]

Changes in intrathoracic pressure have a direct effect on cerebral venous pressure and may alter cerebral perfusion pressure.[22] In order to eliminate this source of error, IPPV was maintained constant and exogenous CO_2 was administered within the fresh gas flow instead of altering the respiratory rate or the tidal volume to achieve the different $EtCO_2$ levels.

TCD was used to measure changes in CBFV and consequently CBF non-invasively. Previous studies have suggested that the diameter of the MCA remains constant during anesthesia[23,24] and that changes in Vmca accurately reflect changes in cerebral blood flow.[25–28] Standard measures for CBF correlate well with CBFV data obtained by TCD in both adults and neonates.[28–30] The insonating angle, i.e., the angle between the ultrasonic beam and the insonated vessel axis, was kept constant throughout the study by using a custom made wheel to fix the TCD probe to the patient's head.[5]

In conclusion, desflurane anesthesia in combination with mild hyperventilation seems to maintain CCO_2R at 1.0 MAC. However, at 1.5 MAC, the effect of hypocapnia on CCO_2R is reduced, probably due to the potent vasodilatatory effect of desflurane. This is also emphasized by the reduction in CCO_2R reported in this study at hypocapnia when compared with the values previously reported for sevoflurane. In children with an increased

ICP the potential benefits of desflurane anesthesia should be weighed carefully against the risks.

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