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Cerebral autoregulation in children during sevoflurane anaesthesia†

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Introduction. Little is known about cerebral autoregulation in children. The aim of this study was to examine cerebral autoregulation in children.

Methods. Cerebral autoregulation testing was performed during less than 1 MAC sevoflurane anaesthesia in children (from 6 months to 14 yr) and in adults (18–41 yr). Mean middle cerebral artery flow velocities (V_{MCA}) were measured using transcranial Doppler ultrasonography. Mean arterial pressure (MAP) was increased to whichever was greater: 20% above baseline or (i) 80 mm Hg for less than 9 yr, (ii) 90 mm Hg for 9–14 yr, and (iii) 100 mm Hg for adults. Cerebral autoregulation was considered intact if the autoregulatory index was $\geqslant$0.4.

Results. There were 13 subjects less than 2 yr old (Group I), 13 subjects 2–5 yr (Group II), 14 subjects 6–9 yr (Group III), 12 subjects 10–14 yr (Group IV), and 12 adults (Group V; control group). All subjects had an autoregulatory index $\geqslant$0.4. There was no difference in autoregulatory index between children in Groups I–IV or between children and adults.

Discussion. We found no age-related differences in autoregulatory capacity during low-dose sevoflurane anaesthesia. We report no differences in autoregulatory capacity between children and adults.

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Cerebral blood flow in adults is said to remain constant between a mean arterial pressure (MAP) of 60 and 160 mm Hg during normocapnia.[1] This process is referred to as cerebral autoregulation. At MAPs outside this range, cerebral blood flow depends on MAP. While it is known that cerebral blood flow varies with age during childhood,[2] little is known about the development and maturation of the autoregulatory capacity in children beyond the neonatal period.

A recent study on dynamic cerebral autoregulation suggests that there may be a difference in autoregulatory capacity between healthy adolescents and healthy adults.[3] In this study, cerebral autoregulation was assessed by observing changes in mean middle cerebral artery flow velocity (V_{MCA}) in response to transient hypotension (dynamic autoregulation testing using thigh cuffs). Cerebral autoregulatory capacity was quantified by computer modelling characterizing the rapidity of return of V_{MCA} to baseline values (before hypotension). The authors reported a difference in autoregulatory capacity in adolescents compared with adults. Confirmation of this difference using a steady-state method of cerebral autoregulation testing was deemed necessary and is the subject of the present study.

Materials and methods

After institutional review board approval, written informed consent for participation in this study was obtained from adult subjects and parents of children. Assent was obtained from children when appropriate. Fifty-five ASA I children 6 months to 14 yr of age and 12 adults 18–41 yr (control group) undergoing general anaesthesia for surgery were enrolled over an 18-month period.

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Experimental protocol

General anaesthesia was administered using a standardized protocol. Patients were pre-medicated with oral midazolam 0.5 mg kg^{-1} as indicated. After placement of standard monitors, general anaesthesia was induced with either i.v. propofol 2 mg kg^{-1}, remifentanil 1.0 μg kg^{-1} and vecuronium 0.1 mg kg^{-1}, or sevoflurane by inhalation. After tracheal intubation, anaesthesia was maintained using age equivalent sevoflurane[4] (less than 1 MAC, end-tidal concentration range 1.7–2.3%) in oxygen 50%/air and a remifentanil infusion at 0.125–1.5 μg kg^{-1} min^{-1}. All patients received mechanical ventilation to maintain normocapnia (Pa_{CO_2} 40 mm Hg).

Invasive arterial pressure recordings were used in subjects when indicated by the surgical procedure and recorded with the transducer at the level of the external auditory meatus (approximating the level of the Circle of Willis). The partial pressure of end-tidal carbon dioxide (E'_{CO_2}) was measured using a capnograph and maintained constant. End-tidal sevoflurane partial pressure was maintained constant for a minimum of 15 min before static autoregulation testing began. Testing was conducted during steady-state surgical stimulation as evidenced by unchanged V_{MCA} for 10 min.[5]

Determination of middle cerebral artery blood flow velocity

All subjects were supine. In each participant, the middle cerebral arteries were insonated by transcranial Doppler ultrasonography (Multidop X; DWL Corp., Sipplingen, Germany) using standard protocols.[6] Using a customized frame, the transducers were secured in place to ensure a constant angle of insonation (Fig. 1).[7] When bilateral V_{MCA}s were obtained, they were averaged for analysis.

Determination of baseline MAP

In inpatients, the median of the MAP recorded 12 h before surgery was used as the baseline MAP. In outpatients, the preoperative MAP was used.

Determination of static cerebral autoregulation

During steady-state anaesthesia, i.v. phenylephrine was titrated using a slow infusion (0.05–0.1 μg kg^{-1} min^{-1}) over a 3–5-min period. In children, MAP was increased to whichever was greater: 20% above the baseline value, or a set value (80 mm Hg for <9-yr age group and 90 mm Hg for the 9–14-yr age group, respectively). In adults, MAP was increased from 80 to 100 mm Hg. MAP and V_{MCA} were simultaneously and continuously recorded and stored in the computer for subsequent offline analysis.

Autoregulatory capacity was quantified using the autoregulatory index, which was calculated according to a previously published formula.[6] Essentially, the autoregulatory index is the per cent change in estimated cerebrovascular resistance (eCVR) per per cent change in MAP:

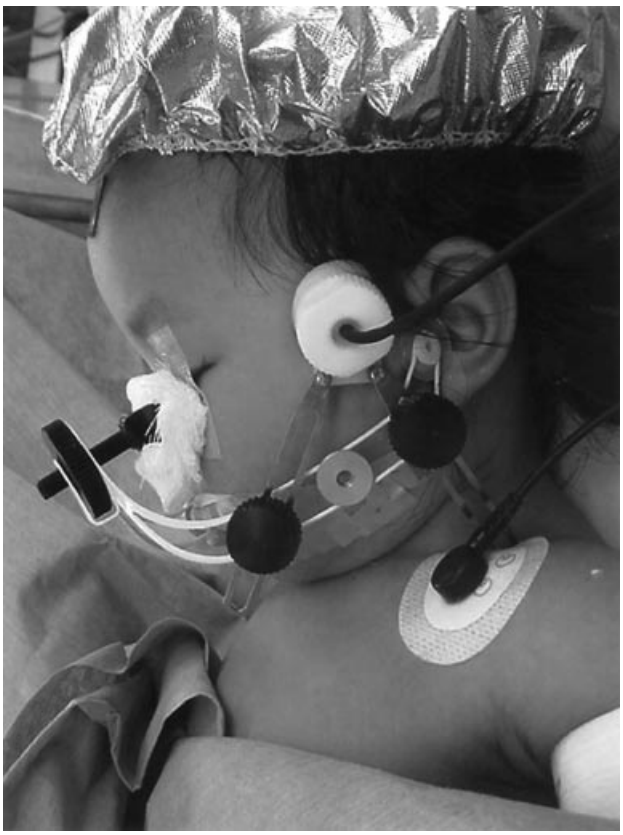

Fig 1 A 6-month-old infant during V_{MCA} measurements and cerebral autoregulation testing. The Lam Rack is used to fix the ultrasound probes during testing.

$$\text{autoregulatory index} = \%\Delta\text{eCVR}/\%\Delta\text{MAP}.$$

The estimated cerebrovascular resistance is the ratio of MAP to V_{MCA}. An autoregulatory index of 0 represents absent autoregulation (pressure-dependent V_{MCA}), whereas an autoregulatory index of 1.0 represents perfect autoregulation. Autoregulatory capacity was considered intact if the autoregulatory index was $\geqslant 0.4$.[6]

Statistical analysis

Subjects were divided into five groups for analysis: (I) <2 yr, (II) 2–5 yr, (III) 6–9 yr, (IV) 10–14 yr, and (V) 18–41 yr. As the normal mean autoregulatory index is 0.75–0.90, and a value of $\geqslant 0.4$ is generally consistent with preserved cerebral autoregulation, a small difference in autoregulatory index would be clinically meaningless. Consequently, we considered a 30% difference in mean autoregulatory index to be significant. Assuming $P<0.05$, $\alpha=0.05$, and $\beta=0.8$, power analysis indicated that we needed 12 subjects in each group for a total of 60 subjects. The influence of age on autoregulatory capacity was examined by comparing the

Table 1 Cross-sectional data of trends by age groups in 65 subjects who underwent static cerebral autoregulation testing: 53 children and 12 adults. Baseline MAP is higher in older children. The average age within each group is given. There is a significant difference in preoperative MAP and middle cerebral artery flow velocity (V_{MCA}) between Groups I and V. V_{MCA} is highest in Group II. Published values based on age appropriate awake V_{MCA}s are 74 (19) (<1 yr), 85 (10) (<3 yr), 94 (10) (<6 yr), 97 (9) (<10 yr), 81 (11) (<17 yr).[2] There is no difference in autoregulatory index (autoregulatory index) between the groups. All children have intact cerebral autoregulation. All values are expressed as mean (SD or range)

Group	I (<2 yr)	II (2–5 yr)	III (6–9 yr)	IV (10–14 yr)	V (18–41 yr)	*P*-value
n=65	13	13	14	13	12	
Age (yr)	1.1 (0.5–1.8)	3.3 (2.0–5.8)	7.3 (6.1–9.8)	13 (10.5–14.7)	29 (19–40)	0.0005
Baseline MAP (mm Hg)	66 (6)	75 (8)	80 (11)	87 (9)	92 (12)	0.001
V_{mca} (cm s^{-1})	69 (14)	97 (24)	73 (7)	57 (5)	50 (10)	0.0008
Autoregulatory index	0.88 (0.20)	0.85 (0.17)	0.85 (0.25)	0.82 (0.26)	0.88 (0.15)	0.74

autoregulatory index in each group (I–IV). The difference in autoregulatory capacity between children and adults was examined by comparing the autoregulatory index in adults (Group V) with each paediatric group and to all children collectively. Each patient's baseline V_{MCA} was compared with previously published age-related normal V_{MCA} values for children without neurological disease.[2] When baseline V_{MCA} was >2 SD of the mean for the age group, they were considered to be hyperdynamic and excluded from further analysis. Analysis of variance, Student's *t*-test, and linear regression analysis were used as appropriate.

Results

Cerebral autoregulation testing was performed in 67 patients: 55 children (37 males and 18 females aged 6 months to 14 yr) and 12 adults (six males and six females aged 18–41 yr) participated in the study. Two children with high baseline V_{MCA} values exhibited low autoregulatory index values; these autoregulatory index values were dramatically different from the rest and were considered outliers. Consequently they were excluded from further analysis and data from 53 of 55 children were used in the final analysis.

There were no complications arising from the studies. The types of paediatric surgical procedures included: excision and grafting of burns (*n*=34), operative reduction and fixation of extremity fractures (*n*=12), exploratory laparotomy for abdominal trauma (*n*=4), and repair of extremity lacerations (*n*=3). The types of adult surgical procedures included excision and grafting of burns (*n*=4) and operative reduction and fixation of extremity fractures (*n*=8). The average duration of the surgery was 1.5 h. Preoperative haematocrit was available in 29 children and in all adults [35 (3) and 37 (2)%, respectively]. All patients maintained normal temperature (>35.5°C) during testing. In 33 children and all adults, the transcranial Doppler ultrasonography signal was obtained from one side only; bilateral measurements were obtained from the remaining 20 children.

There were 13 subjects <2 yr of age (Group I), 13 subjects 2–5 yr of age (Group II), 14 subjects 6–9 yr of age (Group III), and 13 subjects 10–14 yr of age (Group IV). The 12 adults constituted the control group. All subjects in Group I, including the five infants, were born at full-term. The average age within each group is given in Table 1.

V_{MCA} varied significantly with age (ANOVA $P<0.01$) and was highest in Group II. There was no difference in V_{MCA} between children >9 yr of age and adults (Table 1). As expected, there was a linear increase in baseline MAP with increasing age (R^2=0.62, P=0.01), and the combined baseline MAP of Groups III and IV was higher than the combined MAP of Groups I and II (Student's *t*-test; P=0.01). Baseline MAP was higher in adults than in children (Table 1; ANOVA $P<0.01$).

All children and adults had an autoregulatory index $\geqslant 0.4$. The mean autoregulatory index for Groups I, II, III, and IV (children) was 0.88 (0.20), 0.85 (0.17), 0.85 (0.25), and 0.82 (0.26), respectively. The mean autoregulatory index for Group V (adults) was 0.88 (0.15). There was no significant difference in autoregulatory index between Groups I, II, III, and IV, or between children (Groups I–IV) and adults (Group V; P=0.74; Table 1). An illustrative recording of intact cerebral autoregulation is shown in Figure 2.

Discussion

The main findings of this study are: (i) no age-related differences in autoregulatory index were found in our subjects during low-dose sevoflurane anaesthesia and (ii) no differences in autoregulatory index were noted between children and adults. As far as we know, this is the first systematic examination of cerebral autoregulation in children without neurological disease.

Cerebral autoregulation was first demonstrated by Fog who reported a biphasic response of feline pial artery diameter to a sustained change in arterial pressure; decrease in MAP caused immediate vasoconstriction followed by vasodilation within 1–2 min, whereas an increase in MAP caused immediate vasodilation followed by vasoconstriction.[7] It is well known that healthy adults possess the ability to autoregulate cerebral blood flow. Although it is often assumed that the range of MAP over which this compensatory process occurs is consistent among different individuals, considerable variation may exist,[8] and little is known about this process in the paediatric population. Cerebral autoregulation is thought to be impaired in critically ill pre-term neonates and there is debate as to

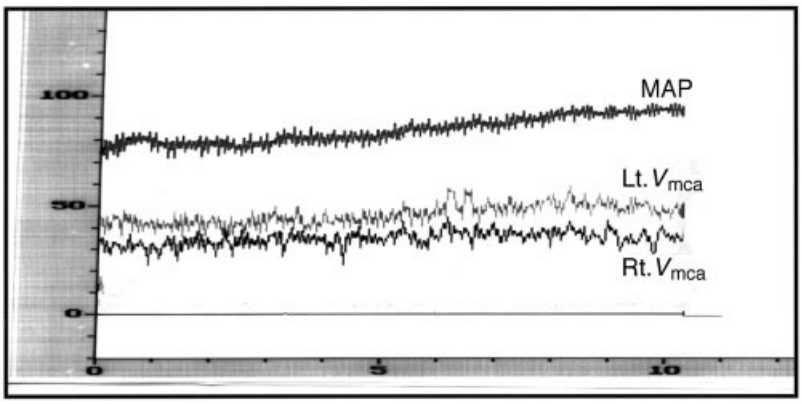

Fig 2 Illustration of intact cerebral autoregulation using transcranial Doppler ultrasonography. Left (Lt) and right (Rt) middle cerebral artery flow velocity (V_{MCA}) remains unchanged despite an increase in MAP.

whether the inability to autoregulate contributes to intraventricular haemorrhage and poor outcome.[10–12] In contrast, it is generally assumed that healthy term infants and children have the ability to autoregulate cerebral blood flow.[13] However, this assumption has not been subjected previously to a formal study.

In the present study, young children demonstrated intact autoregulatory capacity similar to older children and adults. We excluded two children with low autoregulatory index values (0.19 and 0.05) from the final analysis because we considered them outliers. There are two possible explanations for the outliers. First, review of the records reveals that both children had high baseline age-appropriate V_{MCA} values before autoregulation testing. This hyperdynamic state may have been secondary to surgical stimulation and inadequate anaesthesia. Secondly, although an interactive effect between sevoflurane and autoregulatory capacity in children cannot be definitively excluded,[4 14 15] we consider this unlikely as all other children tested had normal autoregulatory index values. Moreover, when we analysed the data with and without the outliers, no difference in autoregulatory index was detected.

In the present study we have demonstrated that V_{MCA} peaks during early childhood and then decreases to near adult values beyond middle childhood. The V_{MCA} values and the age-related differences in V_{MCA} during sevoflurane anaesthesia are similar to what has been reported previously in healthy, awake children.[2] In awake children, V_{MCA} is approximately 40 cm s^{-1} during infancy, increases to a range between 75–110 cm s^{-1} during childhood, and decreases to 50 cm s^{-1} during adolescence.[2] These age-related differences in V_{MCA} appear to be preserved during low-dose sevoflurane. There is, however, no clear explanation for the age-related change in V_{MCA}. Although both the global cerebral metabolic rate for oxygen and for glucose are higher in un-anaesthetized healthy children compared with healthy adults (5.8 *vs* 3.5 and 6.8 *vs* 5.5 ml 100 g brain tissue^{-1} min^{-1}, respectively), the age-related changes in V_{MCA} do not necessarily parallel changes in cerebral metabolic rate.[16 17]

A description of the testing methodology of cerebral autoregulation and the comparative advantages and disadvantages of each method are warranted. Two common techniques used to examine cerebral autoregulation are the (i) static and (ii) dynamic methods of testing. Static autoregulation testing can be considered the 'gold standard' for testing cerebral autoregulation. This involves steady-state elevation or depression of MAP from baseline values, usually pharmacologically. In our study, V_{MCA} was continuously measured and recorded by transcranial Doppler ultrasonography as i.v. phenylephrine was incrementally titrated to increase MAP. The change in V_{MCA} in response to increase in MAP is used to quantify autoregulatory capacity. As testing occurs during steady-state and a plateau of the elevated MAP is maintained, the static method of testing is not dependent on the speed, but only the capacity of the autoregulatory response. In contrast, dynamic autoregulation testing utilizes non-pharmacological means of decreasing MAP. Bilateral thigh cuffs are inflated to 30 mm Hg above the patient's systolic arterial pressure for 3 min and then released. The change in V_{MCA} in response to transient hypotension after cuff deflation is measured, recorded, and analysed to quantify the autoregulatory response. Thus, different ranges of MAP are tested during static and dynamic autoregulation testing. As mentioned, the autoregulatory stimulus in dynamic autoregulation testing is transient hypotension and the autoregulatory capacity is quantified by the rate of return of V_{MCA} to baseline. This technique is attractive for use in children primarily because it is non-invasive. However, there is no control of either the degree of transient hypotension or the duration of hypotension after thigh cuff deflation. The autoregulatory capacity as assessed by dynamic testing is not only influenced by the capacity of the autoregulatory response but also by the latency of the response. Therefore, either an excessive decrease in MAP (below the lower limit of cerebral

autoregulation) or a delay in response in V_{MCA} would appear as an impaired autoregulatory response even though V_{MCA} may return to normal with a sustained decrease in MAP (provided it is above the lower limit of autoregulation).

To clarify the issue of decreased autoregulatory capacity *vs* delayed autoregulatory response in dynamic autoregulation testing, we examined autoregulation in children using static autoregulation testing. For the purposes of this study, we used the autoregulatory index as the measure of autoregulation based on validated studies in healthy adults.[6 18] We tested autoregulation over a narrow range of MAP based on age and published references for upper limits of normal MAP. We chose a slightly higher upper limit for MAP for children ⩾9 years of age because MAP increases with age.[19] In contrast to the study using dynamic autoregulation testing, the present study demonstrates that autoregulatory capacity in children is similar to that of adults. We speculate that the previously observed difference during dynamic autoregulation testing may be attributed to a longer latency response in children.

Transcranial Doppler ultrasonography measures cerebral blood flow velocities in the vessels studied and has been validated for the study of cerebral autoregulation.[20 21] While there are other modalities of studying cerebral blood flow, they are generally more invasive, time consuming, and lack temporal resolution, thereby constraining the study of cerebral haemodynamics in children. Therefore, transcranial Doppler ultrasonography is particularly suited for the study of cerebral autoregulation in children. We were able to insonate only one side in some patients for practical reasons. As good correlation has been shown between left and right V_{MCA}, and our patients were subjects without neurological disease, our autoregulatory index data should remain valid.

There are some limitations to our study. Because our purpose was to study age-related differences in cerebral autoregulation in children, we only performed our studies during low-dose sevoflurane and, as a result, cannot comment on the dose-related effects of sevoflurane on paediatric cerebral autoregulation. To avoid the confounding effects of general anaesthesia, static autoregulation testing needs to be conducted in awake patients. However, this might be impractical in young children. Although remifentanil was used because of ease of titration during surgery and the lack of cerebrovascular effects at the infused doses in adults, an effect of remifentanil on paediatric cerebral autoregulation cannot be ruled out.[22] Although midazolam in adults has been shown to have no significant effects on V_{MCA} and cerebral autoregulation, such an effect in children cannot be excluded.[23] Because of the small number of infants in the present study, we cannot comment on age-related differences in autoregulatory capacity during infancy. Finally, it would have been preferable to use invasive arterial monitoring in all cases, but, again, this poses practical and ethical difficulties, particularly in very young children. In patients where we used non-invasive cuff measurements of arterial pressure, we cycled the cuff every minute during testing. As our patients were healthy, there should be good correlation between MAP obtained via oscillometric arterial pressure monitoring and invasive arterial pressure monitoring. Consequently, we consider our data to be valid.

In conclusion, there were no age-related differences in autoregulatory capacity. Children autoregulated cerebral blood flow similar to adults during low-dose sevoflurane anaesthesia. These findings may be of importance to clinicians managing cerebral haemodynamics in children. Further work is needed to understand the relationship between age, anaesthetic drugs and cerebral autoregulation in healthy and critically ill children.

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