Sevoflurane effects on retrobulbar arteries blood flow in children

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Background. Measure of blood flow velocity in retrobulbar vessels is performed to determine the severity of ophthalmic pathologies as glaucoma. In children, this measure is usually performed under general anaesthesia. Sevoflurane is known to not modify cerebral blow flow velocities. However, its effect on retrobulbar circulation is not known. This study was designed to evaluate the effect of sevoflurane on retrobulbar circulation flow velocity in children undergoing examination for ocular disorders under general anaesthesia.

Methods. Thirteen mechanically ventilated children ($F_{\text{IO}2}=1$) were included. Blood flow velocities of central retinal artery, ophthalmic artery, and middle cerebral artery were measured by Doppler ultrasound during 1 and 2 age-adjusted minimal alveolar concentration (MAC) sevoflurane anaesthesia. Intra-ocular pressure and non-invasive haemodynamic parameters were also measured. End-tidal carbon dioxide tension was controlled during all the study period.

Results. Mean arterial pressure decreased from 1 to 2 age-adjusted MAC sevoflurane (58 [12] vs 54 [12] mm Hg, $P=0.01$). In the ophthalmic artery, end diastolic velocity (EDV) decreased significantly at 2 MAC (1 MAC: 4.4 [4] cm s$^{-1}$ vs 2 MAC: 1.4 [2.4] cm s$^{-1}$; $P=0.04$) and resistivity index (RI) increased significantly (1 MAC: 0.83 [0.11] vs 2 MAC: 0.93 [0.09]; $P=0.007$). Systolic velocity, EDV, and RI remained constant in the central retinal artery and in the middle cerebral artery.

Conclusion. High alveolar concentration of sevoflurane decreased blood flow velocity in the ophthalmic artery, but not in the central retinal and the middle cerebral arteries in children ventilated in hyperoxic condition. This effect was related to a decrease in mean arterial pressure. This vessel-dependant effect may be explained by the different autoregulatory mechanisms of these arteries. In the present hyperoxic conditions, the vascular effect of sevoflurane may have been limited in the central retinal artery and not in the ophthalmic artery.

Keywords: anaesthetics volatile, sevoflurane; blood, flow, velocity; blood, retrobulbar circulation; children

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Sevoflurane is widely used in paediatric patients for mask induction and maintenance of anaesthesia because of its low solubility and its relatively low blood partition coefficient that allows rapid induction and recovery from anaesthesia.1 Sevoflurane effects on cerebral circulation are well characterized. In adults, an increase in sevoflurane administration produces a direct cerebral vasodilation but cerebral blood flow remains constant.2–5 In healthy children, sevoflurane at 1 and 1.5 minimal alveolar concentration (MAC) does not affect cerebral blood flow velocity.5 This lack of cerebrovascular effect is probably related to the preservation of static and dynamic cerebral autoregulation.5

As well as the middle cerebral artery, the ophthalmic artery is a branch of the internal carotid artery. The central retinal artery is a division of the ophthalmic artery. These vessels are involved in the blood supply of the posterior segment, and particularly of the retina. Altered retrobulbar circulation is a frequent finding in ophthalmologic pathology as glaucoma, and these haemodynamic alterations seem to be correlated with the severity of the disease.7 Little is

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known about variations of ocular blood flow during anaesthesia, and case reports of postoperative blindness lead us to consider the importance of the oculo-vascular effect of anaesthetic agents. 

In children with ocular disorders, ocular examination and ultrasound exploration required complete eye immobility and therefore a general anaesthesia. We hypothesized that, in children, sevoflurane could induce retrobulbar haemodynamic variations. This study was therefore designed to evaluate the effect of sevoflurane at 1 and 2 MAC on retrobulbar circulation blood flow velocity in children.

**Patients and methods**

After obtaining approval from the local ethics committee and written informed parental consent, we studied 13 infants and children, ASA physical status I or II, aged 3 months to 5 yr, undergoing elective ocular examination and ultrasound exploration of eyes under general anaesthesia. Patients with neurological, pulmonary, or congenital heart disease were excluded. All received rectal midazolam (0.4 mg kg\(^{-1}\)) as pre-medication 30 min before the procedure. Anaesthesia was induced with sevoflurane in oxygen without nitrous oxide. After tracheal intubation, anaesthesia was maintained with 1 MAC (age-adjusted) sevoflurane in oxygen (100%), and ventilation was adjusted to achieve an end-tidal carbon dioxide pressure at 4.6–5.3 kPa. During the first hour, 25 ml kg\(^{-1}\) of 1% glucose solution was infused, and 4 ml kg\(^{-1}\) thereafter. Non-invasive brachial arterial pressure, electrocardiography, arterial oxygen saturation, and sevoflurane partial pressure were measured continuously. All patients were supine during the procedure. Following stabilization of anaesthesia, patients were allocated to receive either 1 MAC followed by 2 MAC (age-adjusted) of sevoflurane or 2 MAC followed by 1 MAC (age-adjusted) of sevoflurane. Ten minutes of unchanged end-tidal concentration of sevoflurane were required to achieve the steady state for these two different steps. Intra-ocular pressure (IOP) was measured at both MAC level with a hand-held Perkins applanation tonometer (Clement Clarke Inc., Reynoldsburg, OH, USA) by a senior ophthalmologist.

Blood flow velocities of retrobulbar vessels were assessed by colour Doppler imaging using a Sonoline Antares™ ultrasound system (Siemens Medical System Inc., Issaquah, WA, USA). The B-mode frequency was 11.4 MHz and the Doppler frequency 7.3 MHz. A thick layer of gel was applied over the closed superior eyelid. In order not to modify the orbital pressure and therefore the blood vessels haemodynamic characteristics, the probe was not directly applied to the skin. The central retinal vessels were recognized with the colour mode, within the shadow of the optic nerve, and then a small Doppler gate (1.5 or 1.0 mm of width) was positioned 1.5 mm behind the papilla. The ophthalmic artery was recognized with the colour mode at its third portion (before the origin of the central retinal artery) as it runs close to the medial wall of the orbit (posterior and inferior to the superior ophthalmic vein). The same small Doppler gate (1.5 mm of width) was positioned at the most posterior visible part of the vessel. The Doppler gate was not positioned too close to a sinuosity of the vessel.

Cerebral blood flow was assessed by middle cerebral artery flow velocity measurement using a 2 MHz pulsed transcranial Doppler ultrasound (Basic TCD™, Atys Medical, Soucieu en Jarrest, France). The Doppler probe was positioned at the temporal scalp surface, and the M1 segment of the middle cerebral artery was detected as is standard protocol. Repetitive measurements during both anaesthesia levels were performed at the same location of the vessels by the same investigator.

IOP, retrobulbar, and cerebral blood flow Doppler ultrasound were always performed at the side considered as healthy, respectively, by the same ophthalmologist (P.D.), radiologist (O.B.), and anaesthesiologist (T.G.). Peak systolic velocity (PSV) and end diastolic velocity (EDV) were obtained from the spectral mode for ophthalmic, central retinal, and middle cerebral arteries. Resistivity index (RI) was calculated as follow: \(RI = (PSV - EDV)/PSV\). IOP, haemodynamic, and Doppler parameters were measured and recorded by investigators blinded to the MAC value.

Based on a preliminary study showing a 25% decrease of EDV in the ophthalmic artery under 2 MAC sevoflurane anaesthesia compared with 1 MAC, a sample size of 12 patients should be enrolled in the study to show a statistical significant difference with \(\alpha=0.05\) and \(\beta=0.9\) for a two-sided test. After verifying the normal distribution of continuous data, differences between the mean values were analysed using a paired Student’s \(t\)-test. \(P<0.05\) was considered to be statistically significant. All values are expressed as mean (sd).

**Results**

The mean age of the 13 patients was 2.3 yr old (sd 1.5) (range 3 months to 5 yr), and the mean weight 12.8 kg (sd 5.9) (range 2.8–26 kg). Ocular pathologies were: congenital cataract (six), ocular trauma (two), congenital glaucoma (two), intra-ocular haemorrhage (one), pre-term retinopathy (one), and Marfan’s syndrome with ocular disorders (one).

Mean arterial pressure decreased significantly (\(P=0.01\)) at 2 MAC compared with 1 MAC sevoflurane (Table 1). Heart rate and IOP remained unchanged at both sevoflurane concentrations. All patients exhibited an anterograde direction of blood flow in the ophthalmic artery. Blood flow velocities and RI did not change in the middle cerebral and the central retinal arteries. In opposite to these two vessels, EDV decreased (\(P=0.04\)) and RI increased (\(P=0.007\)) significantly at 2 MAC compared with 1 MAC sevoflurane in the ophthalmic artery. Variations of RI, EDV, and PSV for all children are presented in Figure 1. We did not observe any effect of the order of application of the different MAC levels.
Colour Doppler imaging is a non-invasive method to measure blood flow velocity, and it can be used for retrobulbar vessel study.11 This method allows the assessment of blood flow velocity (peak systolic velocity and EDV) in the ophthalmic and the central retinal arteries. In children, retrobulbar arteries blood flow velocities are slower than in adults. Until 5 yr old, in the central retinal artery, PSV is about 6 (3) cm s\(^{-1}\), and in the ophthalmic artery approximately 25–30 cm s\(^{-1}\). In both arteries, the adult values are achieved at around 12 yr old. RI values are not affected by age.12 Changes of local blood flow in this circulation have been used to quantify vascular disorders in pathologies such as glaucoma, diabetes, or carotid artery stenosis.12 In glaucomatous optics neuropathy, many clinical studies confirmed a reduced EDV associated with an elevated RI in the central retinal71 11 31 4 and in the ophthalmic arteries.14 In the absence of intra-ocular hypertension, a high RI value in the ophthalmic artery could be interpreted as a vascular contribution in glaucomatous neuropathy. Doppler examination could be dependent on the investigator, especially for the retrobulbar circulation. However, retrobulbar Doppler

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>1 MAC</th>
<th>2 MAC</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>58 (12)</td>
<td>54 (12)</td>
<td>0.01*</td>
</tr>
<tr>
<td>HR (beats min(^{-1}))</td>
<td>109 (20)</td>
<td>115 (19)</td>
<td>0.08</td>
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<tr>
<td>E(\text{CO}_2) (kPa)</td>
<td>5.3 (0.5)</td>
<td>5.3 (0.5)</td>
<td>0.86</td>
</tr>
<tr>
<td>IOP (mm Hg)</td>
<td>8 (3)</td>
<td>8 (3)</td>
<td>0.43</td>
</tr>
<tr>
<td>(V_{\text{mca}}) (cm s(^{-1}))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSV</td>
<td>95 (24)</td>
<td>97 (22)</td>
<td>0.78</td>
</tr>
<tr>
<td>EDV</td>
<td>40 (18)</td>
<td>36 (16)</td>
<td>0.48</td>
</tr>
<tr>
<td>RI</td>
<td>0.54 (0.12)</td>
<td>0.59 (0.11)</td>
<td>0.19</td>
</tr>
<tr>
<td>(V_{\text{cra}}) (cm s(^{-1}))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSV</td>
<td>4.5 (1.1)</td>
<td>4.2 (1.7)</td>
<td>0.36</td>
</tr>
<tr>
<td>EDV</td>
<td>1.4 (0.7)</td>
<td>1.3 (0.9)</td>
<td>0.37</td>
</tr>
<tr>
<td>RI</td>
<td>0.69 (0.13)</td>
<td>0.70 (0.16)</td>
<td>0.69</td>
</tr>
<tr>
<td>(V_{\text{oa}}) (cm s(^{-1}))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSV</td>
<td>26 (15)</td>
<td>25 (11)</td>
<td>0.82</td>
</tr>
<tr>
<td>EDV*</td>
<td>4.4 (4)</td>
<td>1.4 (2.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>RI*</td>
<td>0.83 (0.11)</td>
<td>0.93 (0.09)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

*P<0.05

Fig 1 Variations for each patient of RI, EDV, and PSV in ophthalmic and central retinal arteries during 1 and 2 MAC sevoflurane anaesthesia.
examination has shown a good short-term reproducibility for the same examiner.\textsuperscript{15} and in our study, it was always performed by the same senior investigator. In this condition, the expected reproducibility coefficient for repeated Doppler measurements in the different orbital arteries is less than 5\% for the RIs and about 10\% for velocity measurements.\textsuperscript{12,15} Moreover, there are variables that could potentially influence ocular circulation and particularly EDV as IOP and carbon dioxide partial pressure. Therefore, carbon dioxide partial pressure was controlled and IOP exhibited no change throughout the application of the different alveolar concentration of sevoflurane.

**Discussion**

In this study, we demonstrate the different effects of sevoflurane on the blood flow of the ophthalmic and the central retinal arteries. Increasing the sevoflurane concentration led to a blood flow decrease in the ophthalmic artery, but not in the central retinal nor in the middle cerebral arteries. This decrease in ophthalmic artery blood flow seems to be related to the decrease in mean arterial pressure.

Effect of inhaled anaesthetic agents on cerebral blood flow are considered as equivalent for all agents. Inhaled anaesthetic agents affect the cerebral circulation in two different ways: a cerebral vasodilatation occurs first by direct effect on vascular smooth muscles of cerebral arteries resulting in increasing blood flow. Secondly, vasoconstriction occurs in relation to the reduction in metabolism. Sevoflurane has the less intrinsic cerebral vasodilatory effect of volatile agents.\textsuperscript{3} At 1.5 MAC, sevoflurane may have a cerebral vasodilatory effect, but human studies using transcranial Doppler showed small changes in cerebral blood flow.\textsuperscript{3} Moreover, sevoflurane maintains cerebral blood flow velocity as constant with increasing MAC in adults and children.\textsuperscript{16} Our study is in accordance with these results even for a high alveolar concentration of sevoflurane as shown by unchanged velocities in the middle cerebral artery despite a decrease in the mean arterial pressure with 2 MAC of sevoflurane.

Ophthalmic artery is the first major branch of the internal carotid artery. The central retinal artery is a subdivision of the ophthalmic artery, and is involved in the blood supply of the posterior segment. Anatomical description of the retrobulbar circulation is presented in Figure 2. Although the oculiculation does not have any autonomic nerve supply, the ophthalmic and central retinal arteries have an autoregulation of their own blood flow.\textsuperscript{17,18} Preservation of this autoregulation is important not only from a physiologic approach, but also for its clinical implications in glaucoma and retinal ischemia.\textsuperscript{19,20} In the ophthalmic artery, previous data suggested a specific and different autoregulative response from the middle cerebral artery: in the case of a non-significant stenosis of the internal carotid artery, vasoreactivity of the ophthalmic artery seems to be lower than in the middle cerebral artery.\textsuperscript{21} In a healthy patient, blood flow velocities of the ophthalmic artery decrease significantly after acetazolamide treatment, in contrast to the middle cerebral or internal carotid arteries.\textsuperscript{19} These results suggest that autoregulation in the ophthalmic artery is different from other cerebral arteries. In the present study, we show a decreased diastolic blood flow velocity in the ophthalmic artery associated with a decrease in the mean arterial pressure induced by sevoflurane anaesthesia. The data suggest that blood flow autoregulation of the ophthalmic artery is impaired by sevoflurane.

In contrast, the central retinal artery appears to be tightly autoregulated, as suggested by the preservation of its blood flow velocities. Central retinal artery blood flow provides about 40\% of retinal oxygen supply. Retinal endothelium derived factors (nitric oxide, prostaglandin, or endothelin) may play a crucial role in the vasomotor tonus in central retinal artery and regulate blood flow with precision.\textsuperscript{22} As in the brain, this efficient autoregulation protects the retina from blood flow variations related to changes in arterial pressure conditions.

Transcranial Doppler ultrasound was used to measure the effect of sevoflurane on cerebral blood flow velocity, as a comparison for ocular blood flow. This non-invasive method is reproducible and has shown a good correlation with a direct measure of cerebral blood flow by xenon clearance or radioactive microsphere.\textsuperscript{23,24} Moreover, transcranial Doppler ultrasound has been validated for the study of cerebral autoregulation in children.\textsuperscript{25-27}

In the present study, patients were ventilated in hyperoxic conditions ($F_{\text{IO}_2}=1$). In animal experimental models in pigs and monkeys, these conditions were associated with the central retinal artery vasoconstriction.\textsuperscript{28,29} The vasoconstriction induced by these hyperoxic conditions may have limited the magnitude of change in blood flow velocity of the central retinal artery. In humans, the hyperoxia-induced retinal vasoconstriction is probably related to endothelin-1 retinal secretion, and is not observed in choroidal circulation.\textsuperscript{30} In young healthy patients, this hyperoxia-induced vasoconstriction is not observed in the ophthalmic artery.\textsuperscript{31} In the present hyperoxic conditions, the vascular effect of sevoflurane may have been limited in central retinal artery but not in ophthalmic artery. A further study concerning the oculo-vascular effects of different $F_{\text{IO}_2}$ levels on these three vessels in anaesthetized children could answer this question.

Effects of i.v. anaesthetic agents (as midazolam or propofol) or of other inhaled agents on retrobulbar circulation are unknown. It could be of interest to study their effects in patients with altered ocular circulation, in whom anaesthesia-related hypotension may severely compromise ocular blood flow.

We concluded that high alveolar concentration of sevoflurane with $F_{\text{IO}_2}=1$ may enhance alterations of ophthalmic artery blood flow diastolic velocity in children but do not alter haemodynamic parameters in central retinal artery. In consequence, interpretation of blood flow velocity values in the retrobulbar circulation (especially in ophthalmic artery)
should consider anaesthesia procedure to avoid excessive diagnosis of vascular disorders in ophthalmic pathologies as glaucoma.

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