Changes in the cerebral arteriovenous oxygen content difference by surgical incision are similar during sevoflurane and isoflurane anaesthesia

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Purpose: To investigate changes of cerebral arteriovenous oxygen content difference (AVDO₂) induced by surgical incision and to determine carbon dioxide (CO₂) reactivity of the cerebral circulation during sevoflurane and isoflurane anaesthesia.

Methods: Twenty-one ASA 1–2 patients undergoing elective surgery for supratentorial tumours were randomly allocated to receive either 1.3 MAC sevoflurane/N₂O anaesthesia (n = 10) or equi-MAC isoflurane/N₂O anaesthesia (n = 11). Before and after incision, haemodynamic measurements and AVDO₂ determinations were performed. After opening the dura, AVDO₂ was determined before and after the respiration rate was increased by 50%.

Results: Incision produced an increase in mean arterial pressure from 69 ± 11 to 97 ± 22 mmHg (mean ± SD) (P < 0.0005) and from 71 ± 6 to 89 ± 12 mmHg (P < 0.0001) in the sevoflurane and isoflurane groups, respectively, whereas the heart rate increased from 60 ± 9 to 72 ± 8 bpm (P < 0.001) and from 65 ± 6 to 70 ± 7 bpm (P < 0.001), respectively. Arterial carbon dioxide tension (PaCO₂) was increased from 33.6 ± 2.3 to 34.6 ± 1.8 mmHg (P < 0.05) with incision in the

sevoflurane group. The AVDO₂ was decreased from 6.5 ± 1.6 to 5.3 ± 1.6 vol% (P < 0.0005) in the sevoflurane group and from 6.7 ± 1.1 to 6.0 ± 1.1 vol% (P < 0.01) in the isoflurane group. The % change of AVDO₂ was larger in the sevoflurane group than in the isoflurane group (–18.3 ± 8.4% vs –9.1 ± 9.0%; P < 0.05) but no difference remained after the post-incisional AVDO₂ value of the sevoflurane group was corrected for pre-incisional PaCO₂. Carbon dioxide reactivity, calculated as the percent change in AVDO₂ per mmHg change in PaCO₂, was 6.1 ± 3.0%·mmHg^{–1} in the sevoflurane group and 5.9 ± 2.4%·mmHg^{–1} in the isoflurane group (P = NS).

Conclusions: Sevoflurane and isoflurane are associated with similar impairment of cerebral flow-metabolism coupling at incision, while CO₂ reactivity is maintained during both anaesthetics.

Objectif: Étudier les changements de la différence artérioveineuse du contenu en oxygène cérébral (AVDO₂) produits par l'incision et déterminer la réactivité au gaz carbonique (CO₂) de la circulation cérébrale sous anesthésie au sévoflurane et à l'isoflurane.

Méthodes: Vingt et un patients ASA 1 et 2 subissant une chirurgie non urgente pour tumeur supratentorielle ont été aléatoirement assignés à recevoir soit une anesthésie au sévoflurane/N₂O 1,3 MAC (n = 10) soit une anesthésie à l'isoflurane/N₂O équivalent-MAC (n = 11). Avant et après l'incision, les mesures hémodynamiques ont été effectuées et AVDO₂ déterminée. Après l'ouverture de la dure-mère, AVDO₂ a été calculée avant et après une augmentation de la fréquence respiratoire de 50%.

Résultats: L'incision a provoqué une augmentation de la pression artérielle moyenne respective de 69 ± 11 à 97 ± 22 mmHg (moyenne ± ET) (P < 0,0005) et 71 ± 6 à 89 ± 12 (P < 0,0001) dans les groupes sévoflurane et isoflurane; la fréquence cardiaque augmentait respectivement de 60 ± 9 à 72 ± 8 bpm (P < 0,001) et de 65 ± 6 à 70 ± 7 bpm (P < 0,001).

Key words

ANAESTHESIA: neurosurgical;
ANAESTHETICS, VOLATILE: sevoflurane; isoflurane;
BRAIN: arteriovenous oxygen content difference, carbon dioxide reactivity.

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Dans le groupe sévoflurane, la PaCO_2 augmentait de $33,6 \pm 2,3$ à $34,6 \pm 1,8$ ($P < 0,05$) avec l'incision. Dans le groupe sévoflurane, AVDO_2 diminuait de $6,5 \pm 1,6$ à $5,3 \pm 1,6$ vol% ($P < 0,0005$) et dans le groupe isoflurane, de $6,7 \pm 1,1$ à $6,0 \pm 1,1$ vol% ($P < 0,01$). Le pourcentage de changement de AVDO_2 était plus important dans le groupe sévoflurane que dans le groupe isoflurane ($-18,3 \pm 8,4\%$ vs $-9,1 \pm 9,0\%$; $P < 0,05$); cette différence est disparue une fois la valeur post-incision du groupe sévoflurane corrigée pour la valeur de PaCO_2 pré-incision. La réactivité du gaz carbonique, calculée en pourcentage de changement en AVDO_2 par mmHg de changement de PaCO_2 était $6,1 \pm 3,0\% \cdot \text{mmHg}^{-1}$ dans le groupe sévoflurane et $5,9 \pm 2,4\% \cdot \text{mmHg}^{-1}$ dans le groupe isoflurane ($P = \text{NS}$).

Conclusion: Le sévoflurane et l'isoflurane sont associés à une perturbation identique du couplage débit-métabolisme à l'incision, alors que la réactivité au CO_2 est maintenue avec les deux anesthésiques.

Sevoflurane is a new volatile anaesthetic that may be a preferred agent for neurosurgery, because its low blood:gas partition coefficient (0.60)¹ promotes faster awakening and allows early postoperative neurological examination. Animal studies have shown that sevoflurane does not increase intracranial pressure in hyperventilated dogs² and that it is indistinguishable from isoflurane with regard to its effects on cerebral haemodynamic variables and metabolism in rabbits.³ A clinical study has shown that this agent effectively maintains the cerebral circulation with respect to carbon dioxide (CO_2) reactivity and autoregulation.⁴

Although sevoflurane and isoflurane appear to have similar effects on cerebral physiology, additional evaluation is required to determine whether sevoflurane is as suitable for neuroanaesthesia as isoflurane, a volatile anaesthetic that has found wide acceptance in neuroanaesthetic practice. Our major concern was to assess whether sevoflurane preserves cerebral flow-metabolism coupling to the same extent as does isoflurane at the time of nociceptive stimulation during surgery. We measured cerebral arteriovenous oxygen content difference (AVDO_2) to assess cerebral flow-metabolism coupling and used surgical incision as the nociceptive stimulation. Then, we studied the changes of AVDO_2 induced by incision during sevoflurane/nitrous oxide (N_2O) anaesthesia and isoflurane/ N_2O anaesthesia in patients with supratentorial tumours. In addition, we determined the CO_2 reactivity of the cerebral circulation during both types of anaesthesia.

Methods

The study was approved by the Hospital Ethics Committee and written informed consent was obtained

from each patient. We studied 21 consecutive ASA physical status 1–2 patients who underwent elective surgery for supratentorial tumours. Patients were randomly allocated to receive either sevoflurane/ N_2O or isoflurane/ N_2O anaesthesia. Patients with decreased consciousness, a midline shift >20 mm on magnetic resonance imaging, cardiopulmonary disease (including hypertension), or a requirement for surgery in the prone position were excluded from the study.

Diazepam 5 mg, *po* and atropine 0.5 mg, *sc* were given as premedication one hour before induction of anaesthesia. With all routine monitors in place (ECG, arterial catheter, pulse oximetry) and after five minutes stabilization, baseline values of mean arterial pressure (MAP) and heart rate (HR) were recorded. Anaesthesia was induced with thiopental 3–4 mg $\cdot \text{kg}^{-1}$, supplemented with fentanyl 2 $\mu\text{g} \cdot \text{kg}^{-1}$. One minute before tracheal intubation, 1.5 mg $\cdot \text{kg}^{-1}$ lidocaine *iv* were given. Tracheal intubation was facilitated with 0.15 mg $\cdot \text{kg}^{-1}$ vecuronium and the lungs were mechanically ventilated to maintain the PETCO_2 concentration between 30 and 35 mmHg (Anaesthetic Gas Monitor, Type 1304, Brüel & Kjaer, Denmark). The rectal temperature (RT) was also monitored. Anaesthesia was maintained with 0.8–1.0 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ fentanyl and N_2O at an end-tidal concentration of 65% (0.6 minimum alveolar concentration (MAC)) in oxygen. In addition, either sevoflurane or isoflurane was given at an end-tidal concentration of 0.7 MAC (Brüel & Kjaer) until the incision was completed. After incision, the concentration of the respective volatile anaesthetic was maintained between 0.5 and 1.5 MAC as necessary until the dura was opened. The MAC of sevoflurane was taken as 1.71%;⁵ of isoflurane as 1.15%;⁶ and of N_2O as 104%.⁷ Intermittent doses of vecuronium *iv* were administered to maintain muscle paralysis. After induction of anaesthesia, a subclavian central venous pressure (CVP) catheter was inserted. The internal jugular bulb on the side contralateral to the major pathology was also cannulated (if the lesion was in the midline, the right side was cannulated) and the catheter tip was confirmed radiographically to be at the level of and just medial to the mastoid process. Normovolaemia was maintained throughout anaesthesia by observing the responses of MAP, HR, and CVP to fluid administration, and colloids and blood products were given as required to maintain a normal CVP.

After at least 20-min stabilization with the respective agent (1.2% sevoflurane or 0.8% isoflurane), surgical incision was performed. Just before and after incision, MAP, HR, and RT were recorded, and blood samples were obtained simultaneously from the jugular and arterial lines for the measurement of AVDO_2 (ABL 505 and OSM 3, Radiometer, Copenhagen, Denmark). Incision

was defined as dissection of the skin, connective tissue, and epicranial aponeurosis or temporal fascia, but not the periosteum of the skull. The AVDO₂ was calculated as the difference in oxygen content between the arterial and jugular venous blood according to the following formula:

$$\text{AVDO}_2 (\text{vol } \%) = 1.39 \times \text{haemoglobin (g} \cdot \text{dl}^{-1}) \times (\text{SaO}_2 - \text{SjvO}_2) (\%) / 100 + 0.003 \times (\text{PaO}_2 - \text{PjvO}_2) (\text{mmHg}),$$

where SaO₂ is the arterial oxygen saturation, SjvO₂ is the jugular venous oxygen saturation, PaO₂ is the arterial oxygen tension, and PjvO₂ is the jugular venous oxygen tension.

Carbon dioxide and oxygen tension data were corrected for the body temperature. The haemoglobin concentration was measured separately (Symex E-4000, Towa, Kobe, Japan).

After the dura was opened and 20 min after 0.7 end-tidal MAC of the test anaesthetic agent with 65% N₂O in oxygen was achieved, the respiratory rate was increased by 50% and the tidal volume was kept constant. Just before and five minutes after the change in ventilation, MAP, HR, and RT were recorded, and blood samples were obtained simultaneously from the jugular and arterial lines for AVDO₂ measurement. The relative CO₂ reactivity⁸ was determined as % $\Delta\text{AVDO}_2/\Delta\text{PaCO}_2$, where the % ΔAVDO_2 is the percent change in AVDO₂ and the ΔPaCO_2 is the difference of arterial CO₂ tension in mmHg.

Data are expressed as the mean $\pm$ SD. The patient characteristics, baseline MAP and HR, the induction dose of thiamylal, the time from induction of anaesthesia to incision, the % change in AVDO₂ upon incision, and CO₂ reactivity were compared by unpaired Student's *t* test. Other data were analyzed by two-way repeated measures of analysis of variance (ANOVA). *P* < 0.05 was taken to indicate statistical significance.

Results

The age, height, weight, sex, midline shift of the tumour, and maximum tumour area were similar in both groups (Table I). All patients were fully conscious before surgery, with four patients in the sevoflurane group and five in the isoflurane group receiving glucocorticoid therapy.

Baseline MAP and HR were 87 ± 10 mmHg and 71 ± 17 bpm in the sevoflurane group and 95 ± 10 mmHg and 74 ± 15 bpm in the isoflurane group (*P* = NS). The induction dose of thiamylal was 3.5 ± 0.3 mg $\cdot$ kg⁻¹ in the sevoflurane group and 3.7 ± 0.4 mg $\cdot$ kg⁻¹ in the isoflurane group (*P* = NS). The time from induction of anaesthesia to incision was 76 ± 17 min in the sevoflurane group and 78 ± 11 min in the isoflurane group (*P* =

TABLE I Patient characteristics (mean $\pm$ SD). The age, sex, height, weight, midline shift of the tumour, and maximum tumour area were similar in both groups

	Sevoflurane group (<i>n</i> = 10)	Isoflurane group (<i>n</i> = 11)
Age (yr) (mean (range))	46 (27–58)	47 (31–64)
Sex (M/F)	6/4	7/4
Height (cm)	160 $\pm$ 9	164 $\pm$ 9
Weight (kg)	59 $\pm$ 13	60 $\pm$ 15
Midline shift (mm)	3 $\pm$ 4	2 $\pm$ 6
Maximum tumour area (cm ²)	8 $\pm$ 5	9 $\pm$ 3

NS). The MAP, HR, PaCO₂, and RT before and after incision also showed no differences between the groups (Table II). Incision increased MAP (*P* < 0.0005 and *P* < 0.0001 in the sevoflurane and isoflurane groups, respectively) and HR (*P* < 0.001) in both groups, and also increased PaCO₂ (*P* < 0.05) in the sevoflurane group. The AVDO₂ was decreased by incision in both groups (*P* < 0.0005 and *P* < 0.01 in the sevoflurane and isoflurane groups, respectively), although the % change in AVDO₂ upon incision was larger in the sevoflurane group ($-18.3 \pm 8.4\%$) than in the isoflurane group ($-9.1 \pm 9.0\%$) (*P* < 0.05).

The MAP, HR, PaCO₂, RT, and AVDO₂ prior to hyperventilation showed no differences between the groups (Table III). After five minutes of hyperventilation, MAP, HR, and RT did not change. Hyperventilation decreased PaCO₂ (*P* < 0.0001) and increased AVDO₂ (*P* < 0.0001) in both groups, but the % $\Delta\text{AVDO}_2/\Delta\text{PaCO}_2$ was not different.

Discussion

In the present study, we determined the changes in AVDO₂ caused by surgical incision. The aim was to assess the anaesthetic stability of cerebral flow-metabolism coupling in the presence of nociceptive stimulation, with the assumption that AVDO₂ reflects the ratio of cerebral metabolic rate for oxygen (CMRO₂) to CBF ($\text{AVDO}_2 = \text{CMRO}_2/\text{CBF}$) and that surgical incision is a representative nociceptive stimulus. We considered that such a study design was clinically relevant for the following reasons. Most previous studies concerning the cerebrovascular and metabolic effects of anaesthesia have been performed under steady state conditions without stimulation, although surgical patients are frequently subjected to various noxious stimuli. Therefore, we felt that it was important to assess not only the effects of anaesthesia on the balance between CMRO₂ and CBF, but also the effects of surgical stimulation on this balance during anaesthesia. Surgical incision may increase the MAP by sympathetic stimulation and an abrupt

TABLE II Physiological variables before and after incision

	MAP (mmHg)	HR (bpm)	PaCO ₂ (mmHg)	RT (°C)	AVDO ₂ (vol %)	Percent change in AVDO ₂ (%)
Sevoflurane group						
Before incision	69 ± 11	60 ± 9	33.6 ± 2.3	36.4 ± 0.5	6.5 ± 1.6	-18.3 ± 8.4
After incision	97 ± 22§	72 ± 8‡	34.6 ± 1.8*	36.3 ± 0.5	5.3 ± 1.6§	
Isoflurane group						
Before incision	71 ± 6	65 ± 6	33.6 ± 2.2	36.4 ± 0.6	6.7 ± 1.1	-9.1 ± 9.0
After incision	89 ± 12¶	70 ± 7‡	33.7 ± 1.9	36.4 ± 0.6	6.0 ± 1.1†	

* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$, § $P < 0.0005$, ¶ $P < 0.0001$ vs before incision. || $P < 0.05$ between the groups. Values are mean ± SD. MAP: mean arterial pressure; HR: heart rate; PaCO₂: arterial carbon dioxide tension; RT: rectal temperature; AVDO₂: cerebral arteriovenous oxygen content difference.

TABLE III Physiological variables before and after hyperventilation

	MAP (mmHg)	HR (bpm)	PaCO ₂ (mmHg)	RT (°C)	AVDO ₂ (vol %)	CO ₂ R (%·mmHg ⁻¹)
<i>Sevoflurane group</i>						
Before hyperventilation	85 ± 13	70 ± 12	33.2 ± 2.1	36.1 ± 0.6	6.0 ± 2.0	6.1 ± 3.0
After hyperventilation	85 ± 13	71 ± 13	27.6 ± 2.6*	36.1 ± 0.6	7.7 ± 2.4*	
<i>Isoflurane group</i>						
Before hyperventilation	76 ± 10	70 ± 10	33.0 ± 2.4	36.2 ± 0.5	6.2 ± 1.1	5.9 ± 2.4
After hyperventilation	76 ± 10	70 ± 10	27.7 ± 2.3*	36.2 ± 0.5	8.0 ± 1.2*	

* $P < 0.0001$ vs before hyperventilation. Values are mean ± SD. PaCO₂: arterial carbon dioxide tension; RT: rectal temperature; AVDO₂: cerebral arteriovenous oxygen content difference; CO₂R: relative carbon dioxide reactivity. The CO₂R was determined as % Δ AVDO₂/ΔPaCO₂, where the % Δ AVDO₂ is the percent change in AVDO₂ and the ΔPaCO₂ is the difference of PaCO₂ in mmHg. There were no differences between the groups.

increase in MAP may be followed by an increase in CBF^{9,10} because cerebral autoregulatory mechanisms are not instantaneously initiated.¹¹⁻¹³ However, an increase in MAP is not the only phenomenon caused by incision, since it may variably increase CMRO₂ and CBF without affecting MAP, depending on the anaesthetic circumstances.¹⁴ In the present study, incision provoked a decrease of AVDO₂ in both groups, indicating that stimulation disturbed the coupling of CMRO₂ with CBF and altered the flow-metabolism balance to a state of relative hyperaemia. Although the % change in AVDO₂ was larger in the sevoflurane group, this was not due to a poor protective effect of sevoflurane anaesthesia against nociceptive stimulation, but rather to the chemically induced increase of CBF (due to increased PaCO₂) upon incision. When the post-incisional AVDO₂ of the sevoflurane group was corrected for the pre-incisional PaCO₂ using the CO₂ reactivity (6.1 ± 3.0 %·mmHg⁻¹), the difference no longer existed. Therefore, sevoflurane anaesthesia appears to be similar to isoflurane anaesthesia with regard to the preservation of coupling during surgical incision.

We calculated CBF reactivity to CO₂ as the %

Δ AVDO₂/ΔPaCO₂.⁸ The validity of the data is dependent on the assumption that if CMRO₂ is constant during hyperventilation, CBF is inversely proportional to AVDO₂.¹⁵ To meet the prerequisite, we obtained data after the dura was opened, because it is a stage when nociceptive stimulation induced by the surgery may be of minor importance and this was supported by the insignificant changes in MAP and HR that occurred during hyperventilation. In addition, hyperventilation *per se* has been reported to have no effect on CMRO₂.¹⁶ We limited hyperventilation to five minutes, assuming that CMRO₂ would be unchanged within this period. Madsen *et al.* measured AVDO₂ changes during hyperventilation, and reported that the relative CO₂ reactivity during 0.75% isoflurane and 67% N₂O/fentanyl anaesthesia was 4.4 ± 2.6 %·mmHg⁻¹ during craniotomy in brain tumour patients.¹⁷ Our patients and mode of anaesthesia were similar to theirs and our isoflurane data (5.9 ± 2.4 %·mmHg⁻¹) were also similar. The slightly higher value obtained in the present study may be ascribed to a slightly different PaCO₂ before hyperventilation (29.7 ± 3.1 mmHg for Madsen *et al.* vs 33.0 ± 2.4 mmHg in our study). A previous study showed that CO₂ reactivity

is well maintained during 0.88 MAC sevoflurane in 33% N₂O in patients with ischaemic cerebrovascular disease.⁴ When the relative CO₂ reactivity was calculated from the normocapnic to hypocapnic range from their study, the value obtained ($6.9 \pm 4.8 \% \cdot \text{mmHg}^{-1}$) is compatible with ours ($6.1 \pm 3.0 \% \cdot \text{mmHg}^{-1}$). Therefore, our results confirmed that CO₂ reactivity was maintained during sevoflurane anaesthesia as well as during isoflurane anaesthesia, and revealed comparable values for the two agents.

Our anaesthetic regimen included fentanyl, N₂O, and an induction dose of thiamylal. We assumed that the effects of thiamylal on cerebral flow-metabolism coupling were minimal, because barbiturates were reported to cause a parallel reduction in CBF and CMRO₂.¹⁸ In addition, the plasma concentration of the drug at the time of incision should have been very low, because the concentration of thiopentone (a barbiturate very similar to thiamylal) is 10% of its peak value 20–30 min¹⁹ after a single intravenous dose. Nitrous oxide may increase both CBF^{20–25} and CMRO₂.^{21,22,24,25} and the degree of increases depends on the anaesthetic regimen.^{22–25} Algotsson *et al.*²⁵ compared the AVDO₂ during anaesthesia with and without N₂O. Changing from 1.7% isoflurane in air/oxygen plus fentanyl anaesthesia to 0.85% isoflurane in 65% N₂O plus fentanyl anaesthesia (equi-MAC) resulted in an increase of CBF and no change of CMRO₂ when PaCO₂ was 4.6 kPa (35 mmHg).²⁵ Therefore, the AVDO₂ values obtained before incision and hyperventilation in our study may be smaller than those during equi-MAC isoflurane/fentanyl anaesthesia without N₂O. Increase in CBF by N₂O is reversed or attenuated by hyperventilation.^{22,23,25} Thus, CBF reactivity to CO₂ is maintained and has been demonstrated in pigs anaesthetized with fentanyl, N₂O, and pancuronium.¹⁶ Cerebral blood flow reactivity is greater during isoflurane anaesthesia than during a MAC-equivalent isoflurane/N₂O anaesthesia.²⁶ Thus, the addition of N₂O during isoflurane/fentanyl anaesthesia might reduce the CO₂ reactivity of the cerebral circulation. However, the applicability of this assumption to sevoflurane/fentanyl anaesthesia could not be determined.

The MAP and HR before and after surgical incision, as well as during hyperventilation, were similar in both groups, findings comparable to results of other studies.^{27,28} There was a small increase of PaCO₂ upon incision in the sevoflurane group. Patients in both groups appeared to be equally anaesthetized at the time of incision, since the thiamylal dose for induction and the induction-incision time were not different between the groups and since both volatile agents were equilibrated at an equi-MAC concentration for 20 min. Thus, either

increased systemic metabolism or increased wasted ventilation upon incision may be responsible for the increase of PaCO₂ in the sevoflurane group. The MAC is determined by motor responses, so equi-MAC conditions do not necessarily indicate that the metabolic response to incision will also be identical.

In summary, surgical incision provoked a similar disturbance of cerebral flow-metabolism coupling to relative hyperaemia during sevoflurane/N₂O and isoflurane/N₂O anaesthesia. We also confirmed that the CO₂ reactivity of the cerebral circulation was well maintained during both types of anaesthesia.

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