

Effect of incremental doses of sevoflurane on cerebral pressure autoregulation in humans

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Summary

We have examined cerebral pressure autoregulation while awake, and during 0.5 and 1.5 MAC of sevoflurane anaesthesia in 10 patients undergoing non-intracranial neurosurgical procedures. All patients received a standardized anaesthetic comprising premedication with temazepam 20 mg orally, a sleep dose of propofol, fentanyl $1 \mu\text{g kg}^{-1}$ and vecuronium 0.1 mg kg^{-1} . After tracheal intubation, the lungs were ventilated with a mixture of air and oxygen to mild hypocapnia. Routine monitors included ECG, continuous and intermittent non-invasive arterial pressure, pulse oximetry and end-tidal capnography. In addition, blood flow velocity (vmca) was measured by insonating the middle cerebral artery transtemporally using a 2-MHz transcranial Doppler probe. Cerebral pressure autoregulation was tested by increasing mean arterial pressure (MAP) by approximately 20 mm Hg using an infusion of phenylephrine and simultaneously recording vmca. The index of autoregulation (IOR) during each period of the study, calculated as the ratio of percentage change in estimated cerebral vascular resistance ($\text{CVR}_e = \text{MAP}/\text{vmca}$) to percentage change in MAP, was compared using ANOVA. vmca during 0.5 and 1.5 MAC of sevoflurane anaesthesia was significantly lower than that while awake (mean 79 (SD 24), 54 (15) and 51 (12) cm s^{-1} , respectively; $P < 0.05$). There was no significant change in vmca with the increase in MAP while awake, or during 0.5 or 1.5 MAC of sevoflurane anaesthesia and IOR was similar under the three conditions (0.82 (0.11), 0.83 (0.04) and 1.0 (0.03), respectively). We conclude that cerebral pressure autoregulation remained intact during sevoflurane anaesthesia in humans. (*Br. J. Anaesth.* 1997; **79**: 469–472).

Key words

Anaesthetics volatile, sevoflurane. Brain, blood flow. Measurement techniques, Doppler ultrasonography.

investigate the effects of incremental doses of the recently introduced inhalation anaesthetic, sevoflurane, on cerebral pressure autoregulation in humans.

Patients and methods

After obtaining local Ethics Committee approval and written informed consent, we studied 10 ASA I or II patients, aged 25–66 yr (mean 48 yr), weighing 52–90 kg (mean 72 kg), undergoing non-intracranial neurosurgical procedures. Patients with neurological, respiratory or cardiovascular disease and those receiving psychotropic drugs were excluded. Patients less than 18 yr of age were also excluded. Routine monitors included ECG, continuous and intermittent non-invasive arterial pressure (Finapres and Dinamap, Ohmeda, USA), pulse oximetry and capnography. In addition, a 2-MHz transcranial Doppler ultrasound probe (DWL Multidop, Sipplingen, Germany) was used to measure the time-averaged mean flow velocity (vmca) in the middle cerebral artery (MCA). The probe was secured in position in a specially designed frame after using standard criteria to obtain the best signal possible from the vessel at a depth of 45–55 mm.⁵ All patients received a standard anaesthetic comprising premedication with temazepam 20 mg orally, propofol 2–2.5 mg kg^{-1} , fentanyl $1 \mu\text{g kg}^{-1}$ and vecuronium 0.1 mg kg^{-1} , and their lungs were ventilated with a mixture of air and oxygen ($F_{\text{I}\text{O}_2}$ 0.35) to maintain mild hypocapnia. Body temperature was maintained greater than 36 °C in all patients using warmed i.v. fluids and a warming blanket. Repeated doses of vecuronium were used to maintain neuromuscular block as required. When necessary, an infusion of phenylephrine was used to maintain mean MAP as close as possible to baseline.

AUTOREGULATION TESTING

Cerebral pressure autoregulation was examined three times in each patient: while awake, during 0.5 and 1.5 MAC of sevoflurane anaesthesia (after

Cerebral pressure autoregulation, a sensitive mechanism impaired in a dose-dependent manner by inhaled anaesthetics, minimizes changes in cerebral blood flow (CBF) when cerebral perfusion pressure changes.^{1–4} This study was designed to

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Table 1 Mean (SD) data during pressure autoregulation testing. * $P < 0.05$ compared with awake; † $P < 0.05$ compared with baseline (ANOVA)

	Awake	0.05 MAC sevoflurane	1.5 MAC sevoflurane
End-tidal CO ₂ (kPa)	5.1 (0.6)	4.5 (0.6)	4.5 (0.5)
Baseline $\dot{v}mca$ (cm s ⁻¹)	79 (24)	54 (15)*	51 (12)*
Autoregulation $\dot{v}mca$ (cm s ⁻¹)	82 (23)	56 (11)*	51 (12)*
Baseline heart rate (beat min ⁻¹)	81 (15)	77 (15)	63 (12)
Autoregulation heart rate (beat min ⁻¹)	60 (12)†	65 (15)†	52 (7)†
Baseline MAP (mm Hg)	95 (10)	86 (12)	85 (13)
Autoregulation MAP (mm Hg)	117 (10)†	109 (14)†	106 (15)†
Change in MAP (mm Hg)	22 (6)	23 (4)	22 (3)
IOR	0.82 (0.11)	0.83 (0.04)	1.0 (0.03)

15 min of unchanged end-tidal concentration and before the start of surgery). Autoregulation was tested by inducing an increase in MAP of approximately 20 mm Hg using an infusion of 0.01% phenylephrine and simultaneously recording $\dot{v}mca$. $\dot{v}mca$ and MAP were used for subsequent calculation of the estimated cerebral vascular resistance ($CVRe = MAP/\dot{v}mca$) at each stage.

The index of autoregulation (IOR), defined as the ratio of percentage change in estimated $CVRe$ to percentage change in MAP, was calculated for each period of the study.⁶ Theoretically, no change in $\dot{v}mca$ should occur if the percentage change in $CVRe$ is equal to the percentage change in MAP. Thus an IOR of 1 implies perfect autoregulation and an IOR of 0, complete disruption of autoregulation. Based on previously published autoregulation data in humans, we considered a change less than 15% in IOR to be clinically insignificant.⁷ Power analysis showed that for a power of 0.8, an alpha error of 0.05 and a beta error of 0.20, the required number of patients to reject the null hypothesis was 10. The computed IOR, and data recorded before and after the phenylephrine-induced increase in MAP, were analysed using ANOVA. $P < 0.05$ was considered significant.

Results

The major findings of the study are shown in table 1. There was no significant change in patient body temperature, arterial saturation or end-tidal carbon dioxide. Mean $\dot{v}mca$ was significantly lower during 0.5 and 1.5 MAC of sevoflurane anaesthesia (79 (SD 24), 54 (15) and 51 (12) cm s⁻¹, respectively) ($P < 0.05$).

Baseline MAP, heart rate and the phenylephrine-induced increase in MAP were similar during the three periods of the study. The phenylephrine-induced increase in MAP did not cause a significant change in $\dot{v}mca$ while awake, or at 0.5 or 1.5 MAC of sevoflurane anaesthesia. Hence, the calculated IOR values were similar during the three periods of the study (0.82 (0.11), 0.83 (0.04) and 1.0 (0.03), respectively).

Discussion

We have shown that sevoflurane did not affect cerebral pressure autoregulation in humans. This is in contrast with other commonly used inhalation agents which abolish autoregulation in a

dose-dependent manner.³ Therefore, a degree of healthy criticism is warranted in order to provide a reasonable explanation for our findings.

Carbon dioxide is a potent cerebral vasodilator. Hypercapnia exhausts the cerebral vasodilator response to changes in perfusion pressure thus reducing autoregulatory capacity.⁸ In contrast, hypocapnia increases cerebral vascular tone resulting in improved cerebral autoregulation.⁹ The end-tidal carbon dioxide concentration during the course of the study remained relatively unchanged at just less than 5 kPa and is unlikely to have significantly influenced the autoregulatory mechanism.

The other drugs used during the study do not have direct cerebrovascular effects. Propofol was used for induction of anaesthesia and most of the induction dose would have undergone re-distribution before autoregulation testing during sevoflurane anaesthesia was commenced. Fentanyl and vecuronium have no direct cerebral vasodilator effects and do not affect cerebral autoregulation.^{10 11}

We used transcranial Doppler ultrasonography (TCD), a non-invasive inexpensive device, as a measure of CBF. Although TCD does not provide a direct measure of CBF, provided the angle of insonation and the diameter of the vessel insonated remain constant, changes in $\dot{v}mca$ accurately reflect relative changes in CBF.¹²⁻¹⁴ We used a frame designed specially to maintain the probe in position, thus ensuring that the angle of insonation remained constant throughout the study. There is also now ample direct and indirect evidence to support the view that the diameter of the MCA does not change significantly with changes in arterial pressure, Pa_{CO_2} or the use of anaesthetic or vasoactive agents.¹³⁻¹⁸

As we measured $\dot{v}mca$ and not absolute CBF, we could only estimate cerebral vascular resistance ($CVRe$). We then calculated the index of autoregulation by dividing the percentage change in $CVRe$ by the percentage change in MAP. This method has been used before as a measure of cerebral autoregulatory capacity.^{3 6} As reported previously, an IOR of 1 indicates that the percentage change in $CVRe$ is the same as the percentage change in MAP and no change in CBF results; perfect autoregulation. Complete absence of autoregulation gives an IOR of 0. The calculated IOR values during 0.5 and 1.5 MAC of sevoflurane anaesthesia were similar to awake values, indicating that cerebral autoregulation remained intact during sevoflurane anaesthesia in humans. Power analysis ensured that 10 patients were sufficient to reject the null hypothesis with a

power of 0.80, an alpha error of 0.05 and a beta error of 0.20, assuming a change less than 15% in the IOR to be clinically insignificant.⁷

Although we examined autoregulation in only one direction (increase in pressure), we chose a level of MAP in the middle of the autoregulation curve. Therefore, there is no reason to assume that a decrease instead of an increase in MAP would have yielded different results. This has been confirmed recently by Tiecks and colleagues who found that the ability of the cerebral circulation to autoregulate was similar if MAP was increased or decreased.¹⁹

We chose to examine the effects of 0.5 and 1.5 MAC of sevoflurane on cerebral pressure autoregulation to allow comparison with published data on other inhalation agents. For example, both isoflurane and desflurane abolish autoregulation at 1.5 MAC.³ Furthermore, it is unlikely that an inhalation agent may be used in neuroanaesthetic practice at concentrations greater than 1.5 MAC.

Our findings are in agreement with the recently published reports on cerebral autoregulation during sevoflurane anaesthesia. Hanel and colleagues have shown that cerebral pressure autoregulation is maintained during 0.5 and 2.0 MAC of sevoflurane anaesthesia in pigs.²⁰ Kitaguchi and colleagues demonstrated that cerebral pressure autoregulation is maintained during 0.88 MAC of sevoflurane anaesthesia in patients with ischaemic cerebrovascular disease undergoing extracranial intracranial bypass.²¹ Cho and co-workers also reported that cerebral pressure autoregulation was maintained during 1.2 MAC of sevoflurane anaesthesia or a mixture of 1.2 MAC of sevoflurane with 60% nitrous oxide in six patients.²² Why should sevoflurane, an agent similar to isoflurane in many of its systemic effects, have a significantly different effect on cerebral autoregulation?

It is generally accepted that the effect of inhalation anaesthetics on the cerebral vasculature is dependent on the balance between their direct cerebral vasodilator action and the indirect vasoconstrictive effect consequent upon normal flow-metabolism coupling.²³ Thus the net effect on CBF of adding an inhalation agent depends on the level of cerebral metabolism before the agent is added. When cerebral metabolism is already depressed, the agent increases CBF by vasodilatation of cerebral vessels. However, if the agent is administered to patients who are in a "light plane of anaesthesia" or awake, its cerebral metabolic depressant effect leads to a decrease in CBF. Hence, while at lower concentrations the major effect on CBF is vasoconstrictive secondary to flow-metabolism coupling, at higher concentrations the direct vasodilator effect predominates with increases in CBF and loss of cerebral autoregulation.²⁴ From recently published data and from work carried out at our institution, it would appear that sevoflurane has a less direct vasodilator effect than either isoflurane or desflurane.^{25,26} Furthermore, work carried out in this institution suggests that the direct vasodilator effect of sevoflurane at 1.5 MAC is approximately 30% of the effect with isoflurane.²⁶ This explains maintenance of autoregulation at 1.5 MAC, as the major effect is

vasoconstriction secondary to flow-metabolism coupling. Hence the cerebral vasculature remains capable of responding to changes in perfusion pressure. Indeed, *vmca* values at 0.5 and 1.5 MAC are in agreement with this hypothesis.

We conclude that cerebral pressure autoregulation was preserved during 0.5 and 1.5 MAC of sevoflurane anaesthesia in humans. This is advantageous for an agent that has many properties favouring its use in neuroanaesthetic practice.

References

1. Miletich DJ, Ivankovich AD, Albrecht RF, Reimann CR, Rosenberg R, McKissic ED. Absence of autoregulation of cerebral blood flow during halothane and enflurane anaesthesia. *Anesthesia and Analgesia* 1976; **55**: 100-105.
2. Smith AI, Neigh JL, Hoffman JC, Wollman H. Effects of general anaesthesia on autoregulation of cerebral blood flow in man. *Journal of Applied Physiology* 1970; **29**: 665-669.
3. Olsen KS, Henriksen L, Owen-Falkenberg A, Dieg-Peterson H, Rosenorn J, Chraemmer-Jorgensen B. Effect of 1 or 2 MAC isoflurane with or without ketanserin on cerebral blood flow autoregulation in man. *British Journal of Anaesthesia* 1994; **72**: 66-71.
4. Strebel S, Lam AM, Matta BF, Mayberg TS, Newell DW. The effect of isoflurane, desflurane and propofol on cerebrovascular pressure autoregulation in humans. *Anesthesiology* 1995; **83**: 66-76.
5. Matta BF, Lam AM, Mayberg TS, Eng CC, Strebel S. The cerebrovascular response to carbon dioxide during sodium nitroprusside- and isoflurane-induced hypotension. *British Journal of Anaesthesia* 1995; **74**: 296-300.
6. Matta BF, Lam AM, Strebel S, Mayberg TS. Cerebral pressure autoregulation and CO₂-reactivity during propofol-induced EEG suppression. *British Journal of Anaesthesia* 1995; **74**: 159-163.
7. Aaslid R, Lindegaard KF, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. *Stroke* 1989; **20**: 45-52.
8. Raichle ME, Stone HL. Cerebral blood flow autoregulation and graded hypercapnia. *European Neurology* 1972; **6**: 1-5.
9. Paulson OB, Olesen J, Christensen MS. Restoration of autoregulation of cerebral blood flow by hypocapnia. *Neurology* 1972; **22**: 286-293.
10. Stirr JA, Maggio W, Haworth C. Vecuronium: effect on intracranial pressure and hemodynamics in neurosurgical patients. *Anesthesiology* 1987; **76**: 570-573.
11. Milde LN, Milde JH, Gallagher WJ. Cerebral effects of fentanyl in dogs. *British Journal of Anaesthesia* 1989; **63**: 710-715.
12. Kirkham FJ, Padayachee TS, Parsons S, Seargent LS, House FR, Gosling RG. Transcranial measurements of blood flow velocities in the basal arteries using pulsed Doppler ultrasound: Velocity as an index of flow. *Ultrasound in Medicine and Biology* 1986; **12**: 15-21.
13. Bishop CCR, Powell S, Rutt D, Brouse NI. Transcranial Doppler measurement of the middle cerebral flow velocity: A validation study. *Stroke* 1986; **17**: 913-915.
14. Giller CA, Bowman G, Dyer H, Mootz L, Krippner W. Cerebral arterial diameters during changes in blood pressure and carbon dioxide during craniotomy. *Neurosurgery* 1993; **32**: 737-741.
15. Newell WD, Aaslid R, Lam AM, Mayberg TS, Winn HR. Comparison of flow and velocity during dynamic autoregulation testing in humans. *Stroke* 1994; **25**: 793-797.
16. Huber P, Handa J. Effects of contrast material, hypercapnia, hyperventilation, hypertonic glucose and papaverine on the diameter of the cerebral arteries—angiographic determination in man. *Investigational Radiology* 1967; **2**: 17-32.
17. Matta BF, Lam AM. Isoflurane and desflurane do not dilate the middle cerebral artery appreciably. *British Journal of Anaesthesia* 1995; **74**: 486P-487P.
18. Matta BF, Mayberg TS, Lam AM. The effect of halothane, isoflurane and desflurane on cerebral blood flow velocity during propofol-induced isoelectric electroencephalogram. *Anesthesiology* 1995; **83**: 980-985.

19. Tiecks FP, Lam AM, Matta BF, Newell DW. Comparison of static and dynamic methods to evaluate impaired cerebral autoregulation. *Stroke* 1995; **26**: 724.
20. Hanel F, Blobner M, Werner C, Bogdanský R, Henke J, Kochs E. Effects of sevoflurane versus isoflurane on cerebral blood flow autoregulation in pigs. *Journal of Neurosurgical Anesthesiology* 1996; **4**: 323S.
21. Kitaguchi K, Ohsumi H, Kuro M, Nakajima T, Hayashi Y. Effects of sevoflurane on cerebral circulation and metabolism in patients with ischemic cerebrovascular disease. *Anesthesiology* 1993; **79**: 704–709.
22. Cho S, Fujigaki T, Uchiyama Y, Fukusaki M, Shibata O, Sumikawa K. Effects of sevoflurane with and without nitrous oxide on human cerebral circulation. *Anesthesiology* 1996; **85**: 755–760.
23. Drummond JC, Todd MM, Scheller MS, Shapiro HM. A comparison of the direct cerebral vasodilating potencies of halothane and isoflurane in the New Zealand white rabbit. *Anesthesiology* 1986; **65**: 462–467.
24. Matta BF, Mayberg TS, Lam AM. Direct cerebrovasodilatory effects of halothane, isoflurane and desflurane during propofol-induced isoelectric encephalogram in humans. *Anesthesiology* 1995; **83**: 980–985.
25. Scheller MS, Nakakimura K, Fleischer JE, Zornow MH. Cerebral effects of sevoflurane in the dog: comparisons with isoflurane and enflurane. *British Journal of Anaesthesia* 1990; **65**: 388–392.
26. Heath K, Gupta S, Matta BF. The effects of sevoflurane on cerebral haemodynamics during propofol anaesthesia. *Anesthesia and Analgesia* 1997; (in press).