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Subanesthetic Concentration of Sevoflurane Increases Regional Cerebral Blood Flow More, but Regional Cerebral Blood Volume Less, than Subanesthetic Concentration of Isoflurane in Human Volunteers

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Summary: Both sevoflurane and isoflurane are used in moderate concentrations in neuroanesthesia practice. The limiting factors for using higher concentrations of inhalational anesthetics in patients undergoing neurosurgery are the agents' effects on cerebral blood flow (CBF) and cerebral blood volume (CBV). In particular, an increase in CBV, which is a key determinant of intracranial pressure, may add to the neurosurgical patient's perioperative risk. To compare the effects of a subanesthetic concentration (0.4 minimum alveolar concentration) of sevoflurane or isoflurane on regional CBF (rCBF), regional CBV (rCBV) and regional mean transit time (rMTT), contrast-enhanced magnetic resonance imaging perfusion measurements were made in spontaneously breathing human volunteers. Absolute changes in rCBF, regional CBV, and rMTT during administration of either drug in regions of interest outlined bilaterally in white and grey matter were nonparametrically (Mann-Whitney test) analyzed. Sevoflurane increased rCBF in practically all regions (absolute change, 4.44 ± 2.87 to 61.54 ± 2.39 mL/100g per minute) more than isoflurane did (absolute change, 12.91 ± 2.52 to 52.67 ± 3.32 mL/100g per minute), which decreased frontal, parietal, and white matter rCBF (absolute change, −1.12 ± 0.59 to −14.69 ± 3.03 mL/100g per minute). Regional CBV was higher in most regions during isoflurane administration (absolute change, 0.75 ± 0.03 to 4.92 ± 0.16 mL/100g) than during sevoflurane administration (absolute change, 0.05 ± 0.14 to 3.57 ± 0.14 mL/100g). Regional mean transit time was decreased by sevoflurane (absolute change, −0.18 ± 0.05 to −0.60 ± 0.04 s) but increased by isoflurane (absolute change, 0.19 ± 0.03 to 0.69 ± 0.04 s). In summary, regional CBV was significantly lower during sevoflurane than during isoflurane administration, although sevoflurane increased rCBF more than isoflurane, which even decreased rCBF in some regions. For sevoflurane and, even more pronouncedly, for isoflurane, the observed changes in cerebral hemodynamics cannot be explained by vasodilatation alone. **Key Words:** Humans—Isoflurane—Regional cerebral blood flow—Regional cerebral blood volume—Regional mean transit time—Sevoflurane

In neuroanesthesia, inhalational anesthetics (for example, sevoflurane and isoflurane) are used to complete balanced anesthesia and to add blood pressure control to total intravenous anesthesia. Although isoflurane has become established as the gold standard for inhalational anesthetics in neuroanesthesia in recent decades, the use of sevoflurane is still a subject of discussion (1,2). Using inhalational anesthetics carries the risk of increased cerebral blood flow (CBF) and volume (CBV), thereby exhausting cerebral compliance and consequently increasing intracranial pressure (3). Therefore, a comparative analysis of isoflurane and sevoflurane with regard to drug-

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specific changes in CBF and CBV is needed before a risk-benefit analysis can be made. In a recent transcranial Doppler ultrasound study, Matta *et al*. (4) showed a stronger intrinsic dose-dependent cerebral vasodilatory effect for isoflurane than for sevoflurane. However, definite statements on changes in CBF and CBV during sevoflurane and isoflurane administration require a comparative, quantitative analysis of regional CBF (rCBF) and CBV (rCBV), which is best performed in the absence of any background medication.

We investigated the effects of subanesthetic (0.4 minimum alveolar concentration [MAC]) concentrations of sevoflurane and isoflurane in human volunteers using contrast-enhanced magnetic resonance imaging (MRI) perfusion measurement, which has the advantage of regional anatomic resolution (5). For a more detailed analysis of changes in rCBV as compared with rCBF, regional mean transit time (rMTT) was used. A relatively greater increase in rCBF than rCBV leads to a decrease in rMTT, whereas a relatively greater increase in rCBV than rCBF causes an increase in rMTT.

METHODS

After approval by the local University Ethics Committee and written informed consent, 20 right-handed, nonsmoking male volunteers (American Society of Anesthesiologists physical status I) with no history of drug or alcohol abuse underwent MRI measurement of contrast-enhanced cerebral perfusion on two consecutive days. Each volunteer was randomized twice: first to determine the order of measurements (control or test-drug), which were separated by 24 hours, and second to receive either sevoflurane (n = 10) or isoflurane (n = 10) as the test drug. Wearing a closely fitting facemask, the volunteers normoventilated (end-tidal carbon dioxide concentration [$PETCO_2$] = 40 mm Hg; fraction of inspired oxygen [FiO_2] = 0.5) during control measurement and inhalation of either sevoflurane (0.4 MAC) (6) or isoflurane (0.4 MAC) (7). A minimum of 15 minutes was allowed for stabilizing end-tidal concentration of either drug. The volunteers had been trained both by verbal instruction and by watching the capnographic trace of the monitor on the day before the MRI session. During the experiment, breathing at a constant $PETCO_2$ (40 mm Hg) was supported by voice command, when necessary. To avoid visual stimuli, all volunteers kept their eyes closed. The fraction of inspired and expired sevoflurane, isoflurane, and oxygen (FiO_2, FeO_2), $PETCO_2$, as well as respiration frequency, were measured. Mean arterial pressure was noninvasively assessed and hemoglobin saturation was monitored with pulsoximetry (Compact, Datex, Helsinki, Finland). Quick Cal calibration gas (Reference 755582; Datex) was used to calibrate the monitor.

Magnetic resonance imaging measurements were performed on a 1.5-tesla whole-body scanner (Magnetom Vision, Siemens, Erlangen, Germany) using a standard circular polarized head coil. Single-shot echo planar imaging was performed with a repetition time of 2 seconds and an echo time of 64 milliseconds. A 64 × 128 acquisition matrix (field of view, 22 × 22 cm; in-plane resolution, 1.7 × 3.4 mm) was used. Slice thickness was set to 5 mm (slice gap, 1.25 mm), and 15 slices were measured simultaneously. A paramagnetic contrast agent (gadolinium–pentaacetic acid, 0.1 mmol/kg) was injected into an antecubital vein at a rate of 9 mL/s using an MR compatible power injector (Spectris, Medrad, Pittsburgh, PA). Echo planar imaging scans (n = 60) were performed at 2-second intervals to cover the entire passage of the contrast agent through the brain.

rCBV and rCBF were calculated by a blinded investigator in regions of interest (ROIs). In each subject, ROIs were outlined free-hand bilaterally in white matter and frontal, parietal, occipital, striatal, and thalamic grey matter on CBV maps (Fig. 1 and 2). Outlining ROIs on corresponding anatomic T2-weighted scans is not possible, as

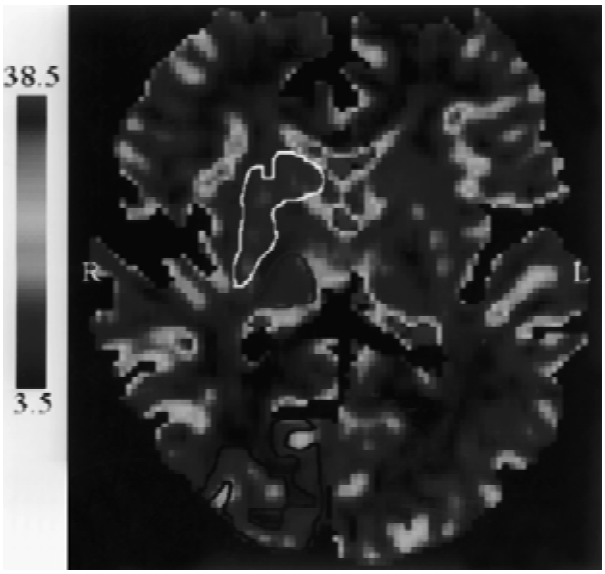

FIG. 1. Representative cerebral blood volume (CBV) map showing regions of interest (ROIs) for evaluation of right hemispheric occipital, striatal, and thalamic grey matter CBV values during administration of isoflurane (0.4 minimum alveolar concentration). R = right hemisphere; L = left hemisphere.

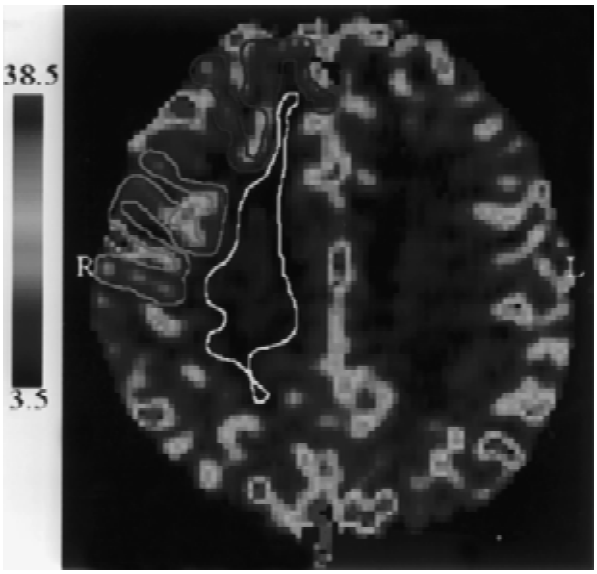

FIG. 2. Representative cerebral blood volume (CBV) map showing regions of interest (ROIs) for evaluation of right hemispheric white matter as well as frontal and parietal grey matter CBV values during administration of isoflurane (0.4 minimum alveolar concentration). R = right hemisphere; L = left hemisphere.

echo planar T2*-weighted contrast-enhanced perfusion scans have a known geometric distortion. To check ROIs for correct anatomic position, they were copied into the echo planar T2*-weighted scans acquired before contrast media application. Corresponding ROIs contained comparable numbers of pixels.

The basic concept used to determine CBV and CBF was previously described by Ostergaard *et al*. (8–10). The impact of arterial input function on contrast-enhanced MRI perfusion measurement was previously shown by Ellinger *et al*. (11). After correction for the density of brain tissue (12), rCBF values are given in mL/100g per minute and rCBV values in mL/100g.

Mean transit time (MTT) (Appendix, Equation 1) defines the average time that any particle of tracer, for example, contrast media, remains within the region of interest (13). Regional mean transit time (rMTT) is given in seconds.

Relative changes in volume

$$\frac{\Delta V}{V} = 2\frac{\Delta R}{R} \qquad [4]$$

(Appendix, Equation 4) and in flow

$$\frac{\Delta F}{F} = \frac{\Delta P}{P} + 2\frac{\Delta V}{V} \qquad [5]$$

(Appendix, Equation 5) are expressed as percentages. In all cases in which the ratio of relative change in flow to relative change in volume (Appendix, Equation 6) does not equal 2, the observed change in flow is not caused solely by the change in radius (vasodilatation).

Statistical Analysis

Data are presented as mean ± SEM. Data were tested for normal distribution using the Kolmogorov-Smirnov Test. For between-group comparisons the Mann-Whitney test was employed. $P \leq .05$ was considered statistically significant.

RESULTS

All 20 volunteers completed the study without complication. Because of motion artefacts, perfusion measurements were not obtainable in one volunteer in the sevoflurane group. All volunteers from both the isoflurane group (n = 10: age 28 ± 5 years, weight: 76 ± 7 kg, height: 177 ± 6 cm) and the sevoflurane group (n = 9; age: 26 ± 4 years, weight: 77 ± 6 kg, height: 179 ± 6 cm) reported severe fatigue and total loss of their sense of space and time. Responsiveness to verbal command, which was necessary once, or at most twice, in each volunteer to maintain normocapnia, was sustained. Contrast-enhanced perfusion measurement was commenced only after verbal command had produced stable normocapnia, so that no further verbal stimulation was needed during perfusion measurement. As overall fluctuations in $PETCO_2$ prompting verbal commands were small (± 5 mm Hg), stable normocapnia of 40 ± 2 mm Hg for 5 minutes was accepted before starting perfusion measurement.

Regional Cerebral Blood Flow

Sevoflurane increased rCBF in all regions studied (absolute change, 4.44 ± 2.87 to 61.54 ± 2.39 mL/100g per minute) (Table 1). In contrast, isoflurane increased rCBF only in striatal, thalamic, and occipital grey matter (absolute change, 12.91 ± 2.52 to 52.67 ± 3.32 mL/100g per minute) (Table 1), and decreased rCBF in white matter and frontal and parietal grey matter (absolute change, −1.12 ± 0.59 to −14.69 ± 3.03 mL/100g per minute). However, except in right occipital grey matter the increase in these regions was significantly less with isoflurane than with sevoflurane. Both inhalational anesthetics increased occipital rCBF more than frontal rCBF.

TABLE 1. *Absolute changes in regional CBF (d-rCBF), regional CBV (d-rCBV) and regional MTT (d-rMTT)*

		Right hemisphere					Left hemisphere				
		Sevoflurane		Isoflurane			Sevoflurane		Isoflurane		
		Mean	SEM	Mean	SEM	*P*	Mean	SEM	Mean	SEM	*P*
WM	d-rCBF	17.35	0.43	−1.64	0.55	*	18.68	0.41	−1.12	0.59	*
	d-rCBV	0.90	0.04	0.75	0.03	*	0.90	0.03	0.91	0.03	ns
	d-rMTT	−0.37	0.03	0.33	0.03	*	−0.52	0.04	0.40	0.04	*
GM_ST	d-rCBF	50.96	2.02	44.55	2.04	*	50.89	2.02	41.27	2.27	*
	d-rCBV	2.36	0.11	3.10	0.09	*	2.32	0.12	2.90	0.09	*
	d-rMTT	−0.32	0.05	0.20	0.03	*	−0.31	0.04	0.19	0.03	*
GM_TH	d-rCBF	40.18	2.63	23.57	2.28	*	44.69	2.61	12.91	2.52	*
	d-rCBV	1.41	0.14	2.95	0.14	*	2.16	0.17	2.74	0.18	*
	d-rMTT	−0.55	0.06	0.36	0.04	*	−0.38	0.05	0.43	0.05	*
GM_FR	d-rCBF	4.44	2.87	−14.69	3.03	*	29.91	2.24	−2.56	3.04	*
	d-rCBV	0.05	0.14	1.99	0.15	*	0.88	0.13	2.95	0.15	*
	d-rMTT	−0.32	0.05	0.53	0.04	*	−0.60	0.04	0.69	0.04	*
GM_PA	d-rCBF	34.47	2.13	−2.20	3.16	*	32.58	2.13	−9.92	2.96	*
	d-rCBV	1.94	0.14	3.32	0.14	*	2.24	0.12	2.83	0.12	*
	d-rMTT	−0.32	0.04	0.64	0.03	*	−0.23	0.05	0.66	0.03	*
GM_OC	d-rCBF	52.74	2.23	52.67	3.32	ns	61.54	2.39	33.96	2.85	*
	d-rCBV	3.29	0.15	4.90	0.14	*	3.57	0.14	4.92	0.16	*
	d-rMTT	−0.18	0.05	0.42	0.05	*	−0.25	0.06	0.66	0.04	*

Absolute change in regional cerebral blood flow (d-rCBF) [mL/100g per minute], absolute change in regional cerebral blood volume (d-rCBV) [mL/100g] and absolute change in regional mean transit time (d-rMTT) [s] in white matter (WM) and in grey matter (striatum (GM_ST), thalamus (GM_TH), frontal (GM_FR), parietal (GM_PA), occipital (GM_OC), during inhalation of sevoflurane (0.4 MAC) (n = 9) or isoflurane (0.4 MAC) (n = 10).

*significant ($P \leq .05$). Data are given as mean ± SEM.

Regional Cerebral Blood Volume

Regional CBV was increased in all regions by both sevoflurane (absolute change, 0.05 ± 0.14 to 3.57 ± 0.14 mL/100g) and isoflurane (absolute change, 0.75 ± 0.03 to 4.92 ± 0.16 mL/100g), and the increase was more pronounced in grey than in white matter (Table 1). Occipital rCBV increased more than parietal or frontal rCBV. Striatal rCBV was greater than frontal rCBV during sevoflurane administration, whereas when using isoflurane, only right hemispheric striatal rCBV was higher than frontal rCBV. In all regions except for left hemispheric white matter, the increase in rCBV was more pronounced for isoflurane than for sevoflurane.

Regional Mean Transit Time

Sevoflurane administration decreased rMTT in all regions studied (absolute change, −0.18 ± 0.05 to −0.60 ± 0.04 s), whereas isoflurane increased rMTT in all regions (absolute change, 0.19 ± 0.03 to 0.69 ± 0.04 s) except in striatal grey matter (Table 1). The decrease for sevoflurane was most pronounced in white matter and less in frontal grey matter, whereas the increase for isoflurane was most pronounced in frontal and parietal grey matter.

The ratio of relative flow change to relative volume change (Appendix, Equation 6) in all regions studied was not equal to 2. Furthermore, in all regions the ratio differed from 2 more strongly when using isoflurane than sevoflurane (Table 2).

Hemodynamic (heart rate, mean arterial pressure) and respiratory (hemoglobin saturation, $PETCO_2$, respiration frequency) parameters were not influenced by either sevoflurane or isoflurane (Table 3).

DISCUSSION

In the current study, sevoflurane and isoflurane each exerted a different effect on rCBF, rCBV, and rMTT. Sevoflurane increased rCBF in all regions studied, whereas isoflurane increased rCBF only in thalamic, striatal, and occipital grey matter, and decreased rCBF in white matter and frontal and parietal grey matter. A similar increase in subcortical rCBF was previously described by Reinstrup *et al*. (14) when measuring thalamic and striatal rCBF in anesthetized patients during isoflurane inhalation (14). In that study the authors found that isoflurane increased rCBF occipitally less than halothane. However, in the current study both isoflurane and sevoflurane increased occipital rCBF more than frontal rCBF. A similar reversal of the normal anterior-posterior gradient in rCBF present in resting-state studies (15) was reported during

TABLE 2. *Hemispheric relative changes in flow (ΔF/F), relative changes in volume (ΔV/V) and the ratio of relative changes in flow and relative changes in volume (ΔF/F/ΔV/V) in right*

	ΔF/F %	ΔV/V %	ΔF/F/ΔV/V	ΔF/F %	ΔV/V %	ΔF/F/ΔV/V
Left H						
WM	33.93	19.26	1.76	−1.48	22.45	−0.07
GM ST	34.19	26.77	1.28	21.76	31.87	0.68
GM_TH	32.55	23.37	1.39	6.36	25.53	0.25
GM_FR	23.03	9.79	2.35	−1.29	29.67	−0.04
GM_PA	23.49	24.14	0.97	−4.86	27.63	−0.18
GM_OC	49.27	38.73	1.27	16.33	44.24	0.37
Right H						
WM	30.01	18.81	1.60	−2.22	18.52	−0.12
GM_ST	36.57	28.07	1.30	23.27	35.13	0.66
GM_TH	30.66	15.47	1.98	13.46	33.17	0.41
GM_FR	3.41	0.56	6.06	−7.70	19.54	−0.39
GM_PA	24.37	19.35	1.26	−1.03	31.34	−0.03
GM_OC	39.44	32.84	1.20	25.91	46.45	0.56

In right (Right H) and left (Left H) hemispheric white matter (WM) and in grey matter (striatum (GM_ST), thalamus (GM_TH), frontal (GM_FR), parietal (GM_PA), occipital (GM_OC) during inhalation of sevoflurane (0.4 MAC)(n = 9) and isoflurane (0.4 MAC) (n = 10). The ratio in all regions did not equal 2, indicating that the observed increase in rCBF is not explained by cerebral vasodilatation alone.

coma (16) and sleep (17), which suggests the reduction of frontal CBF to be a general effect of the altered level of consciousness.

Both inhalational anesthetics increased rCBV, which is the major determinant of an increase in intracranial pressure. To date, little is known about the effects of anesthetic agents on rCBV because of the difficulty of measuring this parameter. Cerebral blood flow (regionally or globally) can be measured more easily and therefore has been used more often to indicate CBV. Changes in CBF, however, do not necessarily indicate parallel changes in CBV of similar magnitude (18). Accordingly, in the current study we found that isoflurane induced a greater increase in rCBV in most regions than sevoflurane, although rCBF was higher during inhalation of sevoflurane.

To further analyze the observed change in rCBF and rCBV, a detailed look at rMTT is essential. Regional mean transit time defines the average time needed by a tracer to transit the ROI (13). Because rMTT equals the ratio of rCBV to rCBF, the decrease in rMTT in the sevoflurane group reflects a relatively greater increase in rCBF than rCBV; in contrast, the increase in rMTT in the isoflurane group reflects a relatively greater increase in rCBV than rCBF.

The effects of inhalational anesthetics on cerebral hemodynamics are determined both by the drug's direct vasodilatory action and the indirect vasodilatory or vasoconstrictive actions caused by flow-metabolism coupling. At doses considerably higher than that used in the current study (1 MAC vs. 0.4 MAC), sevoflurane reduced rCBF (19). Focusing on direct vasodilatory action in anesthetized patients during propofol-induced isoelectric electroencephalography, Matta *et al*. (4) showed isoflurane to be a stronger direct cerebral vasodilatator than sevoflurane.

TABLE 3. *Summary of hemodynamic [heart rate (HR), mean arterial blood pressure (MAP)] and respiratory [pulsoximetry hemoglobin saturation (SpO_2), end-tidal CO_2 concentration ($PETCO_2$), respiration frequency (RF)] parameters during inhalation of sevoflurane (0.4 MAC) (n = 9) and isoflurane (0.4 MAC)(n = 10)*

	HR beats/minute	MAP mm Hg	SpO_2 %	$PETCO_2$ mm Hg	RF breaths/minute
(n = 9)					
Control	63 ± 3	92 ± 2	98 ± 0.4	40 ± 0.1	9 ± 2
Sevoflurane	61 ± 2	89 ± 2	99 ± 0.3	40 ± 0.1	10 ± 1
(n = 10)					
Control	66 ± 2	87 ± 3	99 ± 0.3	40 ± 0.1	11 ± 2
Isoflurane	67 ± 2	91 ± 2	99 ± 0.3	40 ± 0.1	10 ± 2

Data are given as mean ± SEM ($P \leq .05$).

Although there was a considerable loss of sense of space and time in our volunteers during administration of the volatile anesthetic, impairment of consciousness was far from what is found during isoelectric electroencephalography. Therefore, a summed effect of the drug's direct vasodilatatory and indirect flow-metabolism coupling–induced vasodilatory and vasoconstrictive effects can well be assumed in our study. To test this hypothesis, relative changes in rCBF and rCBV during inhalation of sevoflurane and isoflurane were calculated (Table 2). As can be derived from Equation 5 in the Appendix, when only intrinsic vasodilation is present, the ratio of relative change in rCBF and rCBV should equal 2 (Appendix, Equation 6). However, all other cases involve an additional effect (for example, vasoconstriction induced by flow-metabolism coupling). In the current study, both sevoflurane and isoflurane showed this additional effect in all regions. Furthermore, this additional effect was more pronounced for isoflurane than sevoflurane in all regions studied.

A clear limitation of the current study is that metabolic data during inhalation of sevoflurane or isoflurane were not obtainable (for example, by means of phosphate spectroscopy) with the whole-body MR scanner we used. Studies in rats showed that in concentrations of up to 1 MAC, flow-metabolism coupling is preserved during sevoflurane and isoflurane administration (20). From the data obtained in our study, however, it can be stated only that besides a direct vasodilatory action, sevoflurane and, even more pronouncedly, isoflurane exert an additional, indirect metabolic effect on cerebral hemodynamics. This evidence is supported by a previous positron emission tomography study that showed isoflurane to reduce whole-brain glucose metabolism when titrated to a concentration that produced complete loss of consciousness in human volunteers (21).

When comparing the effects of inhalational anesthetics on cerebral hemodynamics, the potential influence on data measurement of cerebral capillary recruitment, cerebral autoregulation, and changes in arterial carbon dioxide tension ($PaCO_2$) must be considered. The hypothesis of capillary recruitment, which was first proposed for frog muscle by Krogh (22) in 1919, states that under resting conditions, most capillaries are contracted and closed to the passage of blood; after stimulation, a large number of capillaries open. Krogh himself, however, did not observe capillary recruitment in the brain, and numerous studies since that time have not produced conclusive evidence for the existence of capillary recruitment in the human brain (23–30). However, because the current study based perfusion measurement on a one-compartment model (8–10), the relationship between rCBF, rCBV, and rMTT also holds true for possible cerebral capillary recruitment.

A few studies have shown that cerebral autoregulation in humans is maintained at 0.5 MAC of sevoflurane (31–33) or isoflurane (34). Neither heart rate nor mean arterial pressure were significantly affected by sevoflurane or isoflurane inhalation, so it is unlikely that activation of cerebral autoregulation led to the observed changes in cerebral hemodynamics. Cerebrovascular reactivity to changes in $PaCO_2$ is also maintained during sevoflurane (33,35) and isoflurane (36,37) administration.

Establishing an arterial line solely for blood gas sampling in our young and otherwise healthy volunteers was not acceptable. Therefore, normocapnia was meticulously controlled by measurement of $PETCO_2$, which correlates well with $PaCO_2$ (38). Thus it is unlikely that $PaCO_2$-induced cerebral vasodilatation influenced rCBF or rCBV measurements during sevoflurane or isoflurane inhalation.

In conclusion, we found that rCBV was significantly lower during sevoflurane (0.4 MAC) than isoflurane (0.4 MAC) administration. Sevoflurane increased rCBF more than isoflurane, which even decreased rCBF in some regions. For sevoflurane and, even more pronouncedly, for isoflurane, the observed changes in cerebral hemodynamics cannot be explained by vasodilatation alone.

APPENDIX

Mean Transit Time (MTT) was calculated with the equation:

$$\mathrm{rMTT} = \frac{rCBV}{rCBF} \cdot 60 \qquad [1]$$

Regional MTT (rMTT) is given in [s].

Flow of a fluid through a tube (under the assumption of linearity) is determined using Hagen-Poseuille's equation:

$$F = \frac{\pi P R^4}{8 L \eta} \qquad [2]$$

where F is the flow, P is the pressure gradient along the tube, R and L are the radius and length of the tube, respectively, and η is the viscosity of the fluid.

The volume of the tube:

$$V = \pi R^2 L \qquad [3]$$

gives a relative change in volume for a change in radius:

$$\frac{\Delta V}{V} = 2\frac{\Delta R}{R} \qquad [4]$$

The relative change in volume $\left(\frac{\Delta V}{V}\right)$ is given in [%].

With equations [3] and [4] we obtain a relative change in flow

$$\frac{\Delta F}{F} = \frac{\Delta P}{P} + 2\frac{\Delta V}{V} \quad [5]$$

whereby the relative change in flow $\left(\frac{\Delta F}{F}\right)$ is given in [%].

If only vasodilatation is present then $\frac{\Delta P}{P} = 0$, and using equation [6] we obtain:

$$\frac{\frac{\Delta F}{F}}{\frac{\Delta V}{V}} = 2 \quad [6]$$

e.g. in all cases in which the ratio of relative change in flow to relative change in volume does not equal 2, the observed change in flow is not due solely to the change in radius (vasodilatation).

$$\frac{\Delta F}{F} = \frac{(rCBFSevoflurane - rCBFControl)}{rCBFControl} \quad [7]$$

$$\frac{\Delta V}{V} = \frac{(rCBVSevoflurane - rCBVControl)}{rCBVControl} \quad [8]$$

$$\frac{\Delta F}{F} = \frac{(rCBFIsoflurane - rCBFControl)}{rCBFControl} \quad [9]$$

$$\frac{\Delta V}{V} = \frac{(rCBVIsoflurane - rCBVControl)}{rCBVControl} \quad [10]$$

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