A Subanesthetic Concentration of Sevoflurane Increases Regional Cerebral Blood Flow and Regional Cerebral Blood Volume and Decreases Regional Mean Transit Time and Regional Cerebrovascular Resistance in Volunteers

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Inhaled anesthetics exert metabolically mediated effects on cerebral blood vessels both directly and indirectly. We investigated the effects of a 0.4 minimum alveolar subanesthetic concentration of sevoflurane on regional cerebral blood flow (rCBF), regional cerebral blood volume (rCBV), regional cerebrovascular resistance (rCVR), and regional mean transit time (rMTT) in volunteers by means of contrast-enhanced magnetic resonance imaging perfusion measurement. Sevoflurane increased rCBF by 16% to 55% (control, 55.03 ± 0.33 to 148.83 ± 1.9 mL · 100 g^{-1} · min^{-1}; sevoflurane, 71.75 ± 0.36 to 193.26 ± 2.14 mL · 100 g^{-1} · min^{-1}) and rCBV by 7% to 39% (control, 4.66 ± 0.03 to 10.04 ± 0.12 mL/100 g; sevoflurane, 5.04 ± 0.03 to 13.6 ± 0.15 mL/100 g); however, sevoflurane decreased rMTT by 7% to 18% (control, 3.75 ± 0.04 to 5.39 ± 0.04 s; sevoflurane, 3.4 ± 0.03 to 4.44 ± 0.03 s) and rCVR by 22% to 36% (control, 0.74 ± 0.01 to 1.9 ± 0.2 mm Hg/[mL · 100 g^{-1} · min^{-1}]; sevoflurane, 0.54 ± 0.01 to 1.41 ± 0.01 mm Hg/[mL · 100 g^{-1} · min^{-1}]). Interhemispheric differences in rCBF, rCBV, and rCVR were markedly reduced after the administration of sevoflurane. These findings are consistent with the known direct vasodilating effect of sevoflurane. The decrease in rMTT further shows that rCBF increases more than does rCBV. Furthermore, we can show that the observed increase in rCBF during inhalation of sevoflurane is not explained by vasodilation alone.

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Although the use of sevoflurane has rapidly increased in anesthesia practice over recent years, its use in neuroanesthesia practice is still the subject of discussion (1,2). Advantages of sevoflurane, such as rapid onset and offset of action, which allow intraoperative titrability (1,3) and rapid postoperative recovery (4), may be overshadowed by the known effects of inhaled anesthetics on cerebral hemodynamics. Vasodilating effects e.g. of halothane (5), enflurane (6), and isoflurane (7) can increase cerebral blood flow (CBF) and cerebral blood volume (CBV), which may adversely affect intracranial pressure. In rabbits, sevoflurane, like isoflurane, was shown to increase CBF and intracranial pressure and to decrease cerebral metabolic rate for oxygen in association with electroencephalographic (EEG) slowing (8). However, reports on the effects of sevoflurane on cerebral hemodynamics in humans are scarce (9–12).

We investigated the influence of a 0.4 minimum alveolar subanesthetic concentration (MAC) of sevoflurane on regional cerebral blood flow (rCBF) and regional cerebral blood volume (rCBV) (13) in humans by means of a contrast-enhanced magnetic resonance imaging (MRI) perfusion measurement, which has the advantage of regional anatomical resolution (14). For a more detailed analysis of changes in rCBV, parallel changes in regional cerebrovascular resistance (rCVR) (15) were calculated. Regional mean transit time (rMTT) was used to analyze relative changes in rCBV compared with rCBF.

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Methods

After approval by our local university ethics committee and written informed consent, 10 right-handed, nonsmoking, male volunteers (ASA physical status I), with no history of drug or alcohol abuse, underwent MRI measurement of contrast-enhanced cerebral perfusion on two consecutive days. Under a closely fitting face mask, the volunteers normoventilated ($ETco_2$ = 40 mm Hg, fraction of inspired oxygen = 0.5) during control measurement and inhalation of sevoflurane (0.4 MAC) (16) in a randomized order. A minimum of 10 to 15 min was allowed for stabilization of end-tidal sevoflurane concentration. The particular dose of 0.4 MAC sevoflurane was chosen because previous studies at our institution proved it to be the largest acceptable dose in spontaneously breathing volunteers. The volunteers were 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 $ETco_2$ (e.g., 40 mm Hg) was supported by voice command when necessary. The fraction of inspired and expired sevoflurane, inspired and expired oxygen, $ETco_2$, respiration frequency (RF), noninvasive mean arterial blood pressure (MAP), and pulsoximetry hemoglobin saturation (Spo_2) were monitored (Compact; Datex, Helsinki, Finland). QUICK CAL™ calibration gas (755582; Datex) was used to calibrate the monitor.

MRI measurements were performed on a 1.5-Tesla whole-body scanner (Magnetom VISION; Siemens, Erlangen, Germany) by using a standard circular polarized head coil. Single-shot echo planar imaging was performed with a repetition time of 2 s and an echo time of 64 ms. An acquisition matrix of 64 × 128 (field of view, 22 × 22 cm; inplane resolution, 1.7 × 3.4 mm) was used. The slice thickness was set to 5 mm (slice gap 1.25), and 15 slices were measured simultaneously. A 0.2 mmol/kg dose of Gd-DTPA, the paramagnetic contrast drug, was injected into an antecubital vein at a rate of 9 mL/s by using a magnetic resonance-compatible power injector (SPECTRIS; Medrad, Pittsburgh, PA). Echo planar imaging scans (n = 60) were performed at 2-s intervals to cover the whole passage of the contrast drug through the brain.

rCBV and rCBF were calculated in regions of interest (ROIs) outlined bilaterally in white and gray (frontal, parietal, occipital, striatal, and thalamic) matter (Figures 1 and 2). The basic concept used to determine CBV and CBF was previously described by Ostergaard et al. (13). The impact of the arterial input function on contrast-enhanced MRI perfusion measurement was shown by Ellinger et al. (17). After correction for the density of brain tissue (18), rCBF values are given in mL · 100 g^{-1} · min^{-1} and rCBV values in mL/100 g. Mean transit time defines the

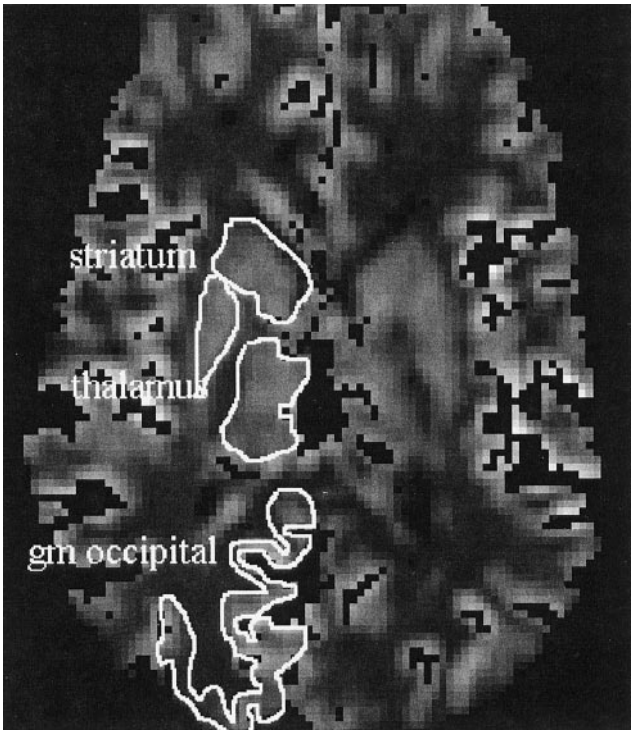

Figure 1. Representative cerebral blood volume map during the administration of 0.4 MAC sevoflurane showing regions of interest for evaluation of right hemispheric thalamic (thalamus), striatal (striatum) and occipital (gm occipital) regional cerebral blood volume.

average time any particle of tracer, e.g., contrast media, remains within the ROI (19) and was calculated with the equation:

$$\text{rMTT} = \frac{rCBV}{rCBF} \times 60 \qquad (1)$$

Regional mean transit time (rMTT) is given in seconds.

Cerebrovascular resistance (CVR) was calculated with the following equation (15,20):

$$\text{rCVR} = \frac{MAP}{rCBF} \qquad (2)$$

Regional CVR (rCVR) is given in mm Hg/(mL · 100 g^{-1} · min^{-1}).

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

$$F = \frac{\pi P R^4}{8 L \eta} \qquad (3)$$

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.

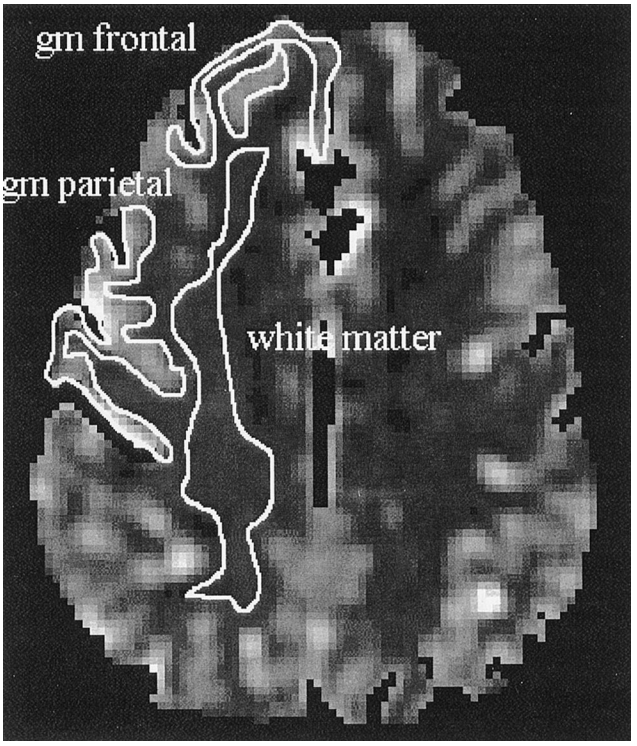

Figure 2. Representative cerebral blood volume map during the administration of 0.4 MAC sevoflurane showing regions of interest for evaluation of right hemispheric white matter (white matter), parietal (gm parietal) and frontal (gm frontal) regional cerebral blood volume.

The volume of the tube:

$$V = \pi R^2 L \tag{4}$$

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

$$\frac{\Delta V}{V} = 2\frac{\Delta R}{R} \tag{5}$$

The relative change in volume ($\Delta V/V$) is given in percentage.

From equations three and four we obtain a relative change in flow:

$$\frac{\Delta F}{F} = \frac{\Delta P}{P} + 2\frac{\Delta V}{V} \tag{6}$$

where by the relative change in flow ($\Delta F/F$) is given in percentage.

If only vasodilation is present, then $\Delta P/P = 0$, and from the previously mentioned equation we obtain:

$$\frac{\frac{\Delta F}{F}}{\frac{\Delta V}{V}} = 2 \tag{7}$$

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 (vasodilation).

$$\frac{\Delta F}{F} = \frac{(rCBFSevoflurane - rCBFControl)}{rCBFControl} \tag{8}$$

$$\frac{\Delta V}{V} = \frac{(rCBVSevoflurane - rCBVControl)}{rCBVControl} \tag{9}$$

Data were presented as mean ± SEM. Data were tested for normal distribution by using the Kolmogoroff-Smirnov test. In the case of normal distribution, analysis of variance for repeated measurements with Bonferroni correction for multiple testing was performed. Otherwise, the Mann-Whitney *U*-test was used. A $P \leq 0.05$ was considered statistically significant.

Results

All volunteers ($n = 10$; age, 26 ± 4 yrs; weight, 77 ± 5 kg; height, 180 ± 6 cm) completed the study without complication. All volunteers reported severe fatigue and total loss of their sense of space and time. Responsiveness to verbal command, which was necessary once, or a maximum of twice, in each volunteer to maintain normocapnia, was sustained. The 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.

Hemodynamic variables (heart rate [control, 63 ± 3 bpm versus sevoflurane, 61 ± 2 bpm], MAP [control, 92 ± 2 mm Hg versus sevoflurane, 89 ± 2 mm Hg]) and respiratory variables Spo_2 (control, 98 ± 0.4% versus sevoflurane, 99 ± 0.3%), $ETco_2$ (control, 40 ± 0.1 mm Hg versus sevoflurane, 40 ± 0.1 mm Hg), and RF (control, 9 ± 2 breaths/min versus sevoflurane, 10 ± 1 breaths/min) were not influenced by sevoflurane.

During control, rCBF ranged from 55.03 ± 0.33 to 148.83 ± 1.9 $mL \cdot 100\ g^{-1} \cdot min^{-1}$. Sevoflurane increased rCBF in all regions studied by 16% to 55% (71.75 ± 0.36 to 193.26 ± 2.14 $mL \cdot 100\ g^{-1} \cdot min^{-1}$) (Table 1). The increase was most pronounced in the occipital gray matter and least pronounced in the parietal gray matter. Occipital rCBF was significantly higher than frontal rCBF during sevoflurane. In white matter, rCBF increased significantly less than in any of the gray matter regions studied, independent of sevoflurane and hemisphere (Table 1). The number of interhemispheric differences in rCBF present at control (white matter and striatal, parietal, and occipital gray matter) was reduced during sevoflurane (thalamic and parietal gray matter) (Table 2).

Table 1. Sevoflurane Increased rCBF and rCBV and Decreased rMTT and rCVR

	Right Hemisphere		Left Hemisphere	
	Control	Sevoflurane	Control	Sevoflurane
WM				
rCBF	57.80 ± 0.34	72.44 ± 0.39	55.03 ± 0.33	71.75 ± 0.36
rCBV	4.78 ± 0.04	5.11 ± 0.03	4.66 ± 0.03	5.04 ± 0.03
rMTT	5.21 ± 0.04	4.41 ± 0.03	5.39 ± 0.04	4.44 ± 0.03
rCVR	1.80 ± 0.01	1.41 ± 0.01	1.90 ± 0.02	1.41 ± 0.01
GM_ST				
rCBF	139.34 ± 1.79	191.85 ± 1.84	148.83 ± 1.90	192.44 ± 1.81
rCBV	8.42 ± 0.10	10.51 ± 0.10	8.67 ± 0.10	10.59 ± 0.09
rMTT	3.91 ± 0.04	3.40 ± 0.03	3.75 ± 0.04	3.42 ± 0.02
rCVR	0.79 ± 0.01	0.57 ± 0.02	0.74 ± 0.01	0.54 ± 0.01
GM_TH				
rCBF	131.02 ± 2.09	164.86 ± 2.45	137.31 ± 2.08	173.46 ± 2.34
rCBV	9.09 ± 0.15	9.69 ± 0.13	9.25 ± 0.14	10.62 ± 0.15
rMTT	4.40 ± 0.06	3.61 ± 0.03	4.28 ± 0.05	3.76 ± 0.03
rCVR	0.85 ± 0.01	0.64 ± 0.01	0.80 ± 0.01	0.61 ± 0.01
GM_FR				
rCBF	130.39 ± 1.81	164.15 ± 1.75	129.78 ± 1.59	163.69 ± 1.63
rCBV	9.70 ± 0.12	10.61 ± 0.11	9.00 ± 0.11	10.29 ± 0.10
rMTT	4.78 ± 0.05	4.07 ± 0.03	4.46 ± 0.04	3.92 ± 0.03
rCVR	0.88 ± 0.01	0.67 ± 0.01	0.91 ± 0.02	0.67 ± 0.01
GM_PA				
rCBF	141.46 ± 1.55	176.74 ± 1.62	139.23 ± 1.69	161.90 ± 1.60
rCBV	10.04 ± 0.12	11.65 ± 0.12	9.31 ± 0.10	10.87 ± 0.11
rMTT	4.50 ± 0.03	4.04 ± 0.03	4.49 ± 0.04	4.18 ± 0.03
rCVR	0.82 ± 0.01	0.61 ± 0.01	0.87 ± 0.01	0.67 ± 0.01
GM_OC				
rCBF	133.91 ± 1.55	190.25 ± 2.09	124.92 ± 1.39	193.26 ± 2.14
rCBV	10.04 ± 0.12	13.06 ± 0.15	9.23 ± 0.11	12.81 ± 0.14
rMTT	4.72 ± 0.04	4.24 ± 0.03	4.66 ± 0.04	4.19 ± 0.04
rCVR	0.86 ± 0.01	0.59 ± 0.01	0.91 ± 0.01	0.58 ± 0.01

rCBF = regional cerebral blood flow (mL · 100 g^{-1} · min^{-1}), rCBV = regional cerebral blood volume (mL/100g), rMTT = regional mean transit time (s), rCVR = regional cerebrovascular resistance (mmHg/ml · 100g^{-1} · min^{-1}), WM = white matter, GM_ST = gray matter striatum, GM_TH = gray matter thalamus, GM_FR = gray matter frontal, GM_PA = gray matter parietal, GM_OC = gray matter occipital.

$P \leq 0.05$ to control measurement in all.

Data are given as mean ± SEM. During the administration of sevoflurane, all parameters (rCBF, rCBV, rMTT, rCVR) were significantly different from control ($P \leq 0.05$).

Regional cerebral blood volume ranged from 4.66 ± 0.03 to 10.04 ± 0.12 mL/100 g. Sevoflurane increased rCBV in all regions by 7% to 39% (5.04 ± 0.03 to 13.06 ± 0.15 mL/100 g). Sevoflurane increased occipital gray matter rCBV most and frontal and thalamic gray matter rCBV least. Occipital rCBV was significantly higher than frontal rCBV. White matter rCBV, which was significantly lower than gray matter rCBV, independent of sevoflurane and hemisphere, was least prone to sevoflurane-induced changes (Table 1). The number of interhemispheric differences present in striatal, frontal, parietal, and occipital gray matter at control was reduced during sevoflurane (Table 2).

Regional mean transit time ranged from 3.75 ± 0.04 to 5.39 ± 0.04 s at control. Sevoflurane decreased rMTT in all regions studied by 7% to 18% (3.4 ± 0.03 to 4.44 ± 0.03 s) (Table 1). The decrease was most pronounced in white matter, whereas it was least pronounced in parietal gray matter as compared with control.

Regional cerebrovascular resistance ranged from 0.74 ± 0.01 to 1.9 ± 0.2 mm Hg/(mL · 100 g^{-1} · min^{-1}). Sevoflurane decreased rCVR in all regions by 22% to 36% (0.54 ± 0.01 to 1.41 ± 0.01 mm Hg/[mL · 100 g^{-1} · min^{-1}]) (Table 1) and reduced the number of interhemispheric differences (Table 2).

The ratio of relative flow change to relative volume change (Equation 7) in all regions studied did not equal 2 (Table 3).

Discussion

Sevoflurane (0.4 MAC) increased rCBF and rCBV; however, it decreased rCVR and rMTT in all regions. Interhemispheric differences in rCBF, rCBV, and rCVR were reduced by sevoflurane.

Before the detailed discussion of our results, the potential influence of cerebral autoregulation and changes in $Paco_2$ on data measurement must be considered. Cerebral autoregulation in humans has been

Table 2. Sevoflurane Decreased the Number of the Hemispheric Differences in rCBF, rCBV, and rCVR

	rCBF	rCBV	rMTT	rCVR
Control				
WM	L < R		L > R	L > R
GM_ST	L > R	L > R	L < R	L < R
GM_TH				
GM_FR		L < R	L < R	
GM_PA	L < R	L < R		L > R
GM_OC	L < R	L < R		L > R
Sevoflurane				
WM				
GM_ST				
GM_TH	L > R	L > R		L < R
GM_FR		L < R	L < R	
GM_PA	L < R	L < R	L > R	L > R
GM_OC			L < R	

rCBF = regional cerebral blood flow, rCBV = regional cerebral blood volume, rMTT = regional mean transit time, rCVR = regional cerebrovascular resistance, WM = white matter, GM_ST = gray matter, striatum; GM_TH = gray matter, thalamus; GM_FR = gray matter, frontal; GM_PA = gray matter, parietal; GM_OC = gray matter occipital; L = left hemispheric, R = right hemispheric.
$P \leq 0.05$.

shown to be maintained up to 1.5 MAC sevoflurane (9,21,22). Neither heart rate nor MAP was significantly affected by sevoflurane inhalation, so it is unlikely that an activation of cerebral autoregulation led to the observed increase in cerebral hemodynamics.

Cerebrovascular reactivity to changes in $Paco_2$ is also maintained during sevoflurane administration (11,22). Normocapnia was meticulously controlled by $ETco_2$ measurement, which correlates well with $Paco_2$ (23), so it is unlikely that $Paco_2$ induced cerebral vasodilation influenced rCBF or rCBV measurements during sevoflurane inhalation.

Iida et al. (24) showed that, at least in part, sevoflurane, as well as isoflurane, induce dilation of cerebral pial vessels in dogs. A cerebral vasodilatory effect of sevoflurane was proposed by Matta et al. (12) from an increase in cerebral blood flow velocity in the middle cerebral artery in patients under propofol/sevoflurane anesthesia. Similarly, in our study a decrease in rCVR during inhalation of sevoflurane, which varied in size according to region, was followed by an increase in rCBV and rCBF.

To further analyze the observed increase 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 (19). Because rMTT equals the ratio of rCBV to rCBF, the observed decrease in rMTT in our volunteers reflects a relatively greater increase in rCBF than in rCBV.

According to Hagen-Poseuille's equation, flow in a tube (vessel) changes with the factor R^4, where R is the radius of the tube (vessel). In contrast, the corresponding volume of the tube (vessel) changes with the factor R^2. Therefore, a relatively greater change in flow than in volume can be expected at a given change of the tube (vessel) radius (R), which consequently decreases rMTT.

However, our analysis of relative changes in volume at a given change of R, and relative changes in flow, clearly demonstrates that the increase in flow is more than would be expected from vasodilation alone (Table 3). Consequently, rMTT decreases more than for solely sevoflurane-induced cerebrovasodilation. Inhaled anesthetics also affect cerebral hemodynamics indirectly by influencing cerebral metabolism (25). It can be assumed that the additional rCBF-increasing effect of small-dose sevoflurane in our study might indicate metabolic changes. It is a limitation of our study that metabolic data during inhalation of sevoflurane (e.g., by means of phosphate spectroscopy) were not obtainable with the whole-body magnetic resonance scanner (Magnetom VISION; Siemens).

However, because coupling of cerebral metabolism and CBF, which is present in awake humans, as well as in patients anesthetized with sevoflurane (26), causes an increase (or decrease) in metabolism to be accompanied by a corresponding change in CBF (25), the observed increase in rCBF, which in our study varied in size according to region (Table 3), might reflect increased metabolism. This is supported by a recent EEG study by Olofson et al. (27) who reported a transient state of cerebral excitation when increasing sevoflurane to 0.5 MAC in patients during the induction of anesthesia.

Moreover, contrary to a simple vasodilatory agent like carbon dioxide which increases rCBF uniformly in all cortical areas (28), sevoflurane showed a marked heterogeneity in the increase in rCBF and rCBV. A similar heterogeneity in rCBF was previously shown for nitrous oxide, which showed a trend to increase anterior and decrease posterior cortical rCBF[1] and isoflurane, which enhanced subcortical (thalamus and basal ganglia) rCBF (30). In contrast, we showed sevoflurane increased rCBF but also rCBV more significantly in occipital, than in frontal gray matter. A similar reversal of the anterior-posterior gradient in rCBF observed in normal resting-state studies (31) was reported during coma (32) and sleep (33), which suggests a reduction of frontal CBF to be a general effect of any state involving an altered level of consciousness.

In an EEG study, Tinker et al. (34) reported that the waking posterior amplitude-dominant EEG pattern shifted to a frontal EEG dominance in Java monkeys when increasing halothane, enflurane, and isoflurane to approximately 0.4 MAC. However, somewhat higher MAC values in the Java monkey than in humans (34) and species differences in the anatomic

[1] Samra SK, Deutsch G, Arens JF. Effect of nitrous oxide on global and regional cerebral blood flow in humans [abstract]. Anesthesiology 1988;69:A536.

Table 3. The Ratio of Relative Flow Change to Relative Volume Change in All Regions Did Not Equal 2, Indicating That the Observed Increase in rCBF Is Not Explained by Cerebral Vasodilatation Alone

	Right Hemisphere			Left Hemisphere		
	$\frac{\Delta F}{F}$ (%)	$\frac{\Delta V}{V}$ (%)	$\frac{\Delta F}{F/\Delta V}$	$\frac{\Delta F}{F}$ (%)	$\frac{\Delta V}{V}$ (%)	$\frac{\Delta F}{F/\Delta V}$
WM	25.32	6.81	3.72	30.38	8.25	3.68
GM_ST	37.68	24.81	1.52	29.31	22.08	1.33
GM_TH	25.83	6.66	3.88	26.32	14.84	1.77
GM_FR	25.89	9.36	2.76	26.13	14.32	1.82
GM_PA	24.94	16.07	1.55	16.28	16.74	0.97
GM_OC	42.07	30.10	1.40	54.71	38.76	1.41

$\Delta F/F$ = hemispheric relative changes in flow, $\Delta V/V$ = relative changes in volume, $\Delta F/F/\Delta V/V$ = ratio of relative changes in flow and relative changes in volume, WM = white matter, GM_ST = gray matter, striatum; GM_TM = gray matter, thalamus; GM_FR = gray matter, frontal; GM_PA = gray matter, parietal; GM_OC = gray matter, occipital.

frontal lobe development between Java monkeys and humans may explain the occipital dominance in rCBF and rCBV increases found during subanesthetic sevoflurane inhalation in our volunteers. A definitive explanation, however, is only possible when EEG measurements, which were not possible in our study, and regional perfusion measurements are taken simultaneously in humans during inhalation of 0.4 MAC of sevoflurane. The number of interhemispheric differences in absolute values of rCBF and rCBV was reduced during inhalation of sevoflurane. As for the existence of asymmetries in rCBF at control in our right-handed, normocapnic volunteers, similar interhemispheric differences in CBF were reported previously in a positron emission tomography (PET) study by Perlmutter et al. (35). To what extent, however, a correlation can be established between sevoflurane-induced changes in consciousness (e.g., loss of sense of space and time) and a decrease in physiologic interhemispheric differences in rCBF must be examined in future studies, which will look not only at rCBF, but also, at regional metabolism and cerebral function (e.g. by means of PET, functional MRI, MR spectroscopy, and EEG). This is supported by examination of propofol-induced loss of consciousness in humans, where concentration-dependent effects on specific neuronal networks (e.g., regulation of arousal, performance of associative functions, and autonomic control) have been found (36). The interhemispheric differences in rCBV we observed, however, can probably be attributed to the better anatomic resolution of MRI and to the fact that MRI-CBV values differ significantly from PET-CBV values (13). The previously shown impact of arterial input function on quantitative evaluation of contrast-enhanced MRI perfusion measurements further illuminates the differences between MRI and PET perfusion values (17).

We found, in humans, that 0.4 MAC of sevoflurane causes regional cerebral vasodilation as rCVR decreases and rCBV increases. Calculation of rMTT showed that rCBF increased relatively more than does rCBV, thereby indicating that the observed increase in rCBF during inhalation of sevoflurane cannot be explained by vasodilation alone.

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References

1. Baker KZ. Desflurane and sevoflurane are valuable additions to the practice of neuroanesthesiology: pro. J Neurosurg Anesthesiol 1997;9:66–8.
2. Tempelhoff R. The new inhalational anesthetics desflurane and sevoflurane are valuable additions to the practice of neuroanesthesia: con. J Neurosurg Anesthesiol 1997;9:69–71.
3. Hormann C, Kolbitsch C, Benzer A. The role of sevoflurane in neuroanesthesia practice. Acta Anaesthesiol Scand Suppl 1997; 111:148–50.
4. Raeder J, Gupta A, Pedersen FM. Recovery characteristics of sevoflurane- or propofol-based anaesthesia for day-care surgery. Acta Anaesthesiol Scand 1997;41:988–94.
5. Albrecht RF, Miletich DJ, Rosenberg R, Zahed B. Cerebral blood flow and metabolic changes from induction to onset of anesthesia with halothane or pentobarbital. Anesthesiology 1977;47: 252–6.
6. Drummond JC, Todd MM, Toutant SM, Shapiro HM. Brain surface protrusion during enflurane, halothane, and isoflurane anesthesia in cats. Anesthesiology 1983;59:288–93.
7. 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;65:462–7.
8. Scheller MS, Tateishi A, Drummond JC, Zornow MH. The effects of sevoflurane on cerebral blood flow, cerebral metabolic rate for oxygen, intracranial pressure, and the electroencephalogram are similar to those of isoflurane in the rabbit. Anesthesiology 1988;68:548–51.
9. Bedford NM, Girling KJ, Harrison JM, Mahajan RP. The effects of sevoflurane and nitrous oxide on middle cerebral artery blood flow velocity and transient hyperemic response. Anesth Analg 1999;89:170–4.
10. Bundgaard H, von Oettingen G, Larsen KM, et al. Effects of sevoflurane on intracranial pressure, cerebral blood flow and cerebral metabolism: a dose-response study in patients subjected to craniotomy for cerebral tumours. Acta Anaesthesiol Scand 1998;42:621–7.
11. Kitaguchi K, Ohsumi H, Kuro M, et al. Effects of sevoflurane on cerebral circulation and metabolism in patients with ischemic cerebrovascular disease. Anesthesiology 1993;79:704–9.

12. Matta BF, Heath KJ, Tipping K, Summors AC. Direct cerebral vasodilatory effects of sevoflurane and isoflurane. Anesthesiology 1999;91:677–80.
13. Ostergaard L, Smith DF, Vestergaard-Poulsen P, et al. Absolute cerebral blood flow and blood volume measured by magnetic resonance imaging bolus tracking: comparison with positron emission tomography values. J Cereb Blood Flow Metab 1998; 18:425–32.
14. Aine CJ. A conceptual overview and critique of functional neuroimaging techniques in humans: I. MRI/FMRI and PET. Crit Rev Neurobiol 1995;9:229–309.
15. Moyer JH, Pontius R, Morris G, Hershberger R. Effect of morphine and n-allylnormorphine on cerebral hemodynamics and oxygen metabolism. Circulation 1957;15:379–84.
16. Mapleson WW. Effect of age on MAC in humans: a meta-analysis. Br J Anaesth 1996;76:179–85.
17. Ellinger R, Kremser C, Schocke M, et al. The impact of the arterial input function (AIF) on quantitative evaluation of dynamic susceptibility contrast enhanced MR studies. Proc ISMR 1998:1207.
18. Brix G, Rempp K, Gueckel F, et al. Quantitative assessment of tissue microcirculation by dynamic contrast-enhanced MR imaging. Adv MRI Contrast 1994;2:68–77.
19. Young WL, Ornstein E. Transit time. In: Cottrell JE, Smith DS, eds. Anesthesia and neurosurgery. St. Louis, MO: CV Mosby, 1994:58.
20. Forster A, Juge O, Morel D. Effects of midazolam on cerebral blood flow in human volunteers. Anesthesiology 1982;56:453–5.
21. Gupta S, Heath K, Matta BF. Effect of incremental doses of sevoflurane on cerebral pressure autoregulation in humans. Br J Anaesth 1997;79:469–72.
22. Cho S, Fujigaki T, Uchiyama Y, et al. Effects of sevoflurane with and without nitrous oxide on human cerebral circulation: transcranial doppler study. Anesthesiology 1996;85:755–60.
23. Campbell FA, McLeod ME, Bissonnette B, Swartz JS. End-tidal carbon dioxide measurement in infants and children during and after general anaesthesia. Can J Anaesth 1994;41:107–10.
24. Iida H, Ohata H, Iida M, et al. Isoflurane and sevoflurane induce vasodilation of cerebral vessels via ATP-sensitive K+ channel activation. Anesthesiology 1998;89:954–60.
25. Hansen TD, Warner DS, Todd MM, Vust LJ. The role of cerebral metabolism in determining the local cerebral blood flow effects of volatile anesthetics: evidence for persistent flow-metabolism coupling. J Cereb Blood Flow Metab 1989;9:323–8.
26. Kuroda Y, Murakami M, Tsuruta J, et al. Preservation of the ration of cerebral blood flow/metabolic rate for oxygen during prolonged anesthesia with isoflurane, sevoflurane, and halothane in humans. Anesthesiology 1996;84:555–61.
27. Olofsen E, Dahan A. The dynamic relationship between end-tidal sevoflurane and isoflurane concentrations and bispectral index and spectral edge frequency of the electroencephalogram. Anesthesiology 1999;90:1345–53.
28. Maximilian VA, Prohovnik I, Risberg J. Cerebral hemodynamic response to mental activation in normo- and hypercapnia. Stroke 1980;11:342–7.
29. Deleted in proof.
30. Reinstrup P, Ryding E, Algotsson L, et al. Distribution of cerebral blood flow during anesthesia with isoflurane or halothane in humans. Anesthesiology 1995;82:359–66.
31. Prohovnik I, Hakansson K, Risberg J. Observations on the functional significance of regional cerebral blood flow in "resting" normal subjects. Neuropsychologia 1980;18:203–17.
32. Deutsch G, Eisenberg HM. Frontal blood flow changes in recovery from coma. J Cereb Blood Flow Metab 1987;7:29–34.
33. Townsend RE, Prinz PN, Obrist WD. Human cerebral blood flow during sleep and waking. J Appl Physiol 1973;35:620–5.
34. Tinker JH, Sharbrough FW, Michenfelder JD. Anterior shift of the dominant EEG rhythm during anesthesia in the Java monkey: correlation with anesthetic potency. Anesthesiology 1977;46:252–9.
35. Perlmutter JS, Powers WJ, Herscovitch P, et al. Regional asymmetries of cerebral blood flow, blood volume, and oxygen utilization and extraction in normal subjects. J Cereb Blood Flow Metab 1987;7:64–7.
36. Fiset P, Paus T, Daloze T, et al. Brain mechanisms of propofol-induced loss of consciousness in humans: a positron emission tomographic study. J Neurosci 1999;19:5506–13.