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Sevoflurane and nitrous oxide increase regional cerebral blood flow (rCBF) and regional cerebral blood volume (rCBV) in a drug-specific manner in human volunteers

Christian Kolbitsch[a,*], Ingo H. Lorenz[a], Christoph Hörmann[a], Christian Kremser[b], Michael Schocke[b], Stephan Felber[b], Patrizia L. Moser[d], Martin Hinteregger[a], Karl P. Pfeiffer[c], Arnulf Benzer[a]

[a]*Department of Anaesthesia and Intensive Care Medicine, University of Innsbruck, Austria*
[b]*Department of Magnetic Resonance Imaging, University of Innsbruck, Austria*
[c]*Department of Biostatistics and Documentation, University of Innsbruck, Austria*
[d]*Department of Pathology, University of Innsbruck, Austria*

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Abstract

Anesthesia for diagnostic procedures, e.g., MRI measurements, has increasingly used sevoflurane and nitrous oxide in recent years. Sevoflurane and nitrous oxide are known cerebrovasodilatators, however, which potentially interferes with MRI examination of cerebral hemodynamics. To compare the effects of relevant equianesthetic concentrations (0.4 MAC) of both drugs on regional cerebral blood flow (rCBF) and regional cerebral blood volume (rCBV) we used contrast-enhanced magnetic resonance imaging (MRI) perfusion measurement, which has the advantage of providing regional anatomic resolution.

Sevoflurane increased rCBF more than did nitrous oxide in all regions except in parietal and frontal gray matter. Nitrous oxide, by contrast, increased rCBV in most of the gray matter regions more than did sevoflurane. In summary we show that, in contrast to nitrous oxide, sevoflurane supratentorially reversed the anterior-posterior gradient in rCBF and typically redistributed rCBF to infratentorial gray matter. In contrast, nitrous oxide increased rCBV more than did sevoflurane. Both inhalational anesthetics had a drug-specific influence on cerebral hemodynamics, which is of importance when interpreting MRI studies of cerebral hemodynamics in anesthetized patients.

Keywords: Sevoflurane; Nitrous oxide; Regional CBF; Regional CBV; Humans

1. Introduction

While rapid onset, intraoperative titrability and rapid offset have prompted the increasing use of sevoflurane in anesthesia in recent years [1], nitrous oxide has a long tradition in the field of anesthesia [2]. The anesthetic use of both inhalational agents for diagnostic procedures, e.g., MRI measurements, has become common practice [1]. Both sevoflurane [3] and nitrous oxide [4] are cerebrovasodilatators, however, which has implications for MRI examination of cerebral hemodynamics. A comparative analysis of both drugs with respect to their effects on cerebral hemodynamics, e.g., cerebral blood flow (CBF) and cerebral blood volume (CBV) at concentrations relevant during balanced anesthesia for MRI diagnostic procedures, has not yet been conducted.

We therefore designed the study at hand to compare the effects of 0.4 minimum alveolar concentration (MAC) of sevoflurane or nitrous oxide on regional cerebral blood flow (rCBF) and regional cerebral blood volume (rCBV) in human volunteers by means of contrast-enhanced magnetic resonance imaging (MRI) perfusion measurement, which has the advantage of providing regional anatomic resolution [5].

2. Methods

Following approval by the local University Ethics Committee and written informed consent, twenty right-handed,

* Corresponding author. Tel.: +43/(0)512/504/2400; fax: +43/(0)512/504/2450.

E-mail address: christian.kolbitsch@uibk.ac.at (C. Kolbitsch).

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non-smoking male volunteers (ASA physical status I) with no history of any drug or alcohol abuse underwent MRI measurement of contrast-enhanced cerebral perfusion on two consecutive days. Wearing a closely fitting face mask the volunteers normoventilated (end-tidal carbon dioxide concentration (EtCO2) = 40 mmHg, FiO2 = 0.5) during control measurement and administration of sevoflurane (0.4 MAC) [6] ($n = 10$) or nitrous oxide (0.4 MAC) [6] ($n = 10$) in random order. A minimum of 10 to 15 min was allowed for stabilization of 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 prior to the MRI session. During the experiment, breathing at a constant EtCO2 (e.g., 40 mm Hg) was supported by voice command when necessary. The fraction of inspired and expired sevoflurane, nitrous oxide, oxygen (FiO2, FeO2), EtCO2, respiration frequency (RF), noninvasive mean arterial blood pressure (MAP) and pulsoximetry hemoglobin saturation (SpO2) were monitored (Compact, Datex, Finland). QUICK CAL™ calibration gas (REF: 755582; Datex, Finland) was used to calibrate the monitor.

MRI measurements were performed on a 1.5-Tesla whole-body scanner (Magnetom VISION, Siemens, Germany) using a standard circular polarized head coil. Single-shot echo planar imaging (EPI) was performed with a repetition time (TR) of 2s and an echo time (TE) of 64 ms. An acquisition matrix of 64 × 128 (field of view (FOV) 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 paramagnetic contrast agent Gd-DTPA (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 Inc., Pittsburgh, PA, USA). EPI scans ($n = 60$) were performed at 2s intervals to cover the entire passage of the contrast agent through the brain. Six scans (6/60 scans) taken preinjection were used as the baseline.

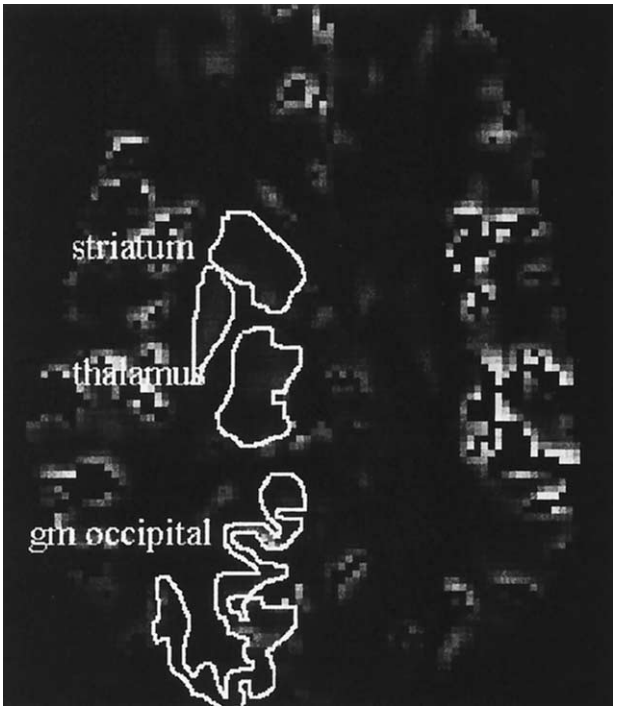

Fig. 1. Representative cerebral blood volume (CBV) map showing regions of interest (ROIs) for evaluation of right hemispheric thalamic (thalamus), striatal (**striatum**) and occipital (**gm occipital**) regional cerebral blood volume (rCBV).

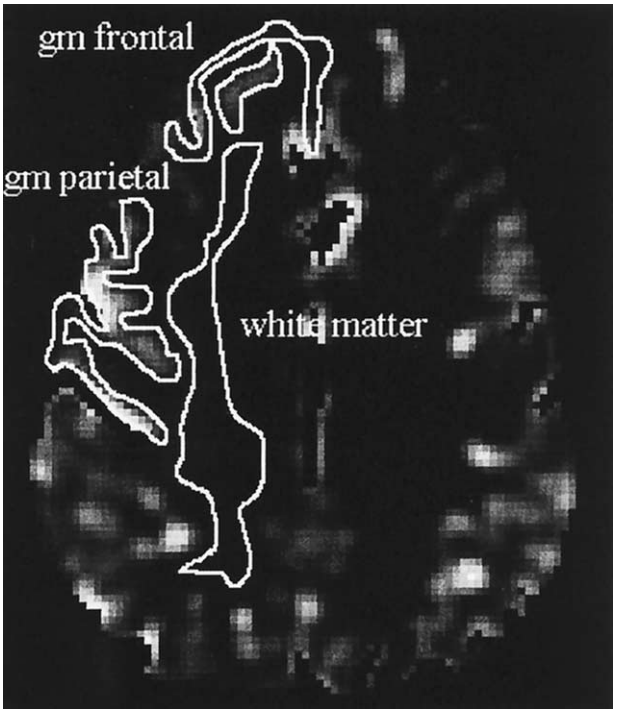

Fig. 2. Representative CBV map showing regions of interest (ROIs) for evaluation of right hemispheric white matter (**white matter**), parietal (**gm parietal**) and frontal (**gm frontal**) regional cerebral blood volume (rCBV).

rCBV and rCBF were calculated by a blinded investigator in regions of interest (ROIs) outlined bilaterally in white and in (frontal, parietal, occipital, striatal and thalamic) gray matter (Figs. 1 and 2). Outlining ROIs on corresponding anatomic T_2-weighted scans is not possible as EPI (echo planar imaging) T2*-weighted contrast-enhanced perfusion scans have a known geometric distortion. In order to check the ROIs for correct anatomic position, they were copied into the EPI T2*-weighted scans acquired before contrast media application. The definition of regions produced in this way is reliable and reproducible and is not biased to high signal areas on the CBV maps. Furthermore, varying partial volume effects from white and gray matter inclusion in regions accorded primarily to one category, which could account for some of the differences between the regions, were minimized. Corresponding ROIs contained comparable numbers of pixels.

The basic concept used to determine CBV and CBF was previously described by Ostergaard et al. [7,8,9].

In brief: Based on a one compartment model to describe

Table 1
Summary of side effects observed during administration of sevoflurane (0.4 MAC) (n = 9) and of nitrous oxide (0.4 MAC) (n = 9).

	Sevoflurane (n = 9)	Nitrous oxide (n = 9)
Loss of sense of time	9 (9)	9 (9)
Loss of sense of space	9 (9)	9 (9)
Sensation of warmth	9 (9)	0 (9)
Relaxation	8 (9)	0 (9)
Fatigue	9 (9)	0 (9)
Discomfort	0 (9)	2 (9)
Giggling	0 (9)	5 (9)
Laughter	0 (9)	3 (9)
Focused mental activity	0 (9)	8 (9)
Nausea	0 (9)	1 (9)
Vomiting	0 (9)	0 (9)
Amplification of sound	0 (9)	9 (9)

the passage of the paramagnetic contrast agent through the brain tissue, the tissue concentration of the contrast agent, c_{tis} (t), can be expressed as:

$$C_{tis}(t) = CBF \cdot AIF(t) \otimes R(t) \quad (1)$$

$\otimes$ denotes the convolution operator and R(t) is the residue function, which describes the fraction of injected contrast agent still present in the tissue at time t. Equation (1) is the central equation to determine CBF using nondiffusible tracers. Singular value decomposition is able to calculate CBF from Eq. (1) with good accuracy, independently of the underlying vascular structure. CBV can be determined by integrating the tissue concentration-time curve, c_{tis} (t), and normalizing with the integral of AIF:

$$CBV = k_H \cdot \frac{\int C_{tis}(t)dt}{\int AIF(t)dt} \quad (2)$$

where k_H is a correction factor ($k_H \approx 0.73$).

An improved gamma variate fit was used to reduce underestimation of the arterial input function (AIF), which otherwise leads to overestimation of CBV and CBF values [31].

Following correction for the density of brain tissue [11] rCBF values are given in [mL/100g/min] and rCBV values in [mL/100g].

2.1. Statistical analysis

Data are presented as mean ± SEM. Data were tested for normal distribution using the Kolmogorov-Smirnov Test. Analysis of variance (ANOVA) for repeated measurements with Least-Square-Difference (LSD) correction for multiple testing was performed. A $p \leq 0.05$ was considered statistically significant.

3. Results

All volunteers ($n = 20$; age: 26 ± 1 years; weight: 77 ± 1 kg; height: 179 ± 1 cm) completed the study without complication, but motion artifacts prevented measurements from being obtained in volunteer No. 2 from the nitrous oxide group and volunteer No. 6 from the sevoflurane group.

All volunteers ($n = 18$) reported impairment of their sense of space and time. None reported unpleasant sensations during inhalation of sevoflurane ($n = 9$). Most enjoyed inhalation of nitrous oxide, although some (2/9) found it uncomfortable. All ($n = 9$) experienced amplification of sound during inhalation of nitrous oxide (Table 1).

Responsiveness to verbal command, which was necessary once or maximum twice in each volunteer in order to maintain normocapnia, was sustained in both groups. 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 (heart rate, MAP) and respiratory (SpO2, EtCO2, RF) parameters were influenced neither by sevoflurane nor by nitrous oxide (Table 2).

Table 2
Summary of hemodynamic (heart rate (HR), mean arterial blood pressure (MAP)) and respiratory (pulsoximetry hemoglobin saturation (SpO2), end-tidal CO2 concentration (EtCO2), respiration frequency (RF)) parameters during administration of sevoflurane (0.4 MAC) (FiO2 = 0.5) and of nitrous oxide (0.4 MAC) (FiO2 = 0.5).

	HR beats/minute	MAP mmHg	SpO2 %	EtCO2 mmHg	RF breaths/min
(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.l	10 ± 1
(n = 9)					
Control	75 (±13)	92 (±11)	98 (±0.3)	39 (±1.0)	12 (±4)
Nitrous oxide	70 (±16)	98 (±10)	98 (±0.2)	39 (±0.7)	11 (±2)

*Significant ($p \leq 0.05$). Data are given as mean ± SEM.

Table 3
Synopsis of data collected at baseline (O2/Air, FiO2 = 0.5) (n = 18) and during administration of sevoflurane (0.4 MAC) (FiO2 = 0.5) (n = 9) or nitrous oxide (0.4 MAC) (FiO2 = 0.5) (n = 9) in white matter (WM) and in grey matter (striatum (GM_ST), thalamus (GM_TH), frontal (GM_FR), parietal (GM_PA), occipital (GM_OC)). Regional cerebral blood flow (rCBF) is given in [mL/100 g/min] and regional cerebral blood volume (rCBV) in [mL/100 g]

		Right Hemisphere								Left Hemisphere							
		Baseline		Sevoflurane			Nitrous Oxide			Baseline		Sevoflurane			Nitrous Oxide		
		Mean	SEM	Mean	SEM	p	Mean	SEM	p	Mean	SEM	Mean	SEM	p	Mean	SEM	p
WM	rCBF	51.80	0.26	70.73	0.42	*	54.27	0.56	*	48.94	0.25	70.25	0.40	*	50.60	0.55	*
	rCBV	4.57	0.03	5.17	0.03	*	4.89	0.05	*	4.44	0.02	5.13	0.03	*	4.50	0.05	n.s.
GM_ST	rCBF	129.64	1.42	187.51	1.84	*	146.57	2.64	*	140.31	1.52	192.45	1.78	*	143.40	2.43	n.s.
	rCBV	8.11	0.08	10.25	0.10	*	11.50	0.20	*	8.61	0.09	10.54	0.09	*	11.24	0.18	*
GM_TH	rCBF	125.82	1.70	164.75	2.44	*	113.81	2.23	*	129.2	1.56	173.03	2.39	*	128.86	2.34	n.s.
	rCBV	8.93	0.12	9.71	0.13	*	10.38	0.18	*	9.24	0.11	10.68	0.15	*	11.11	0.2	*
GM_FR	rCBF	123.69	1.55	161.04	1.80	*	154.79	2.67	*	120.95	1.29	160.42	1.69	*	174.21	3.16	*
	rCBV	9.66	0.10	10.55	0.11	*	13.76	0.18	*	8.99	0.09	10.26	0.10	*	13.91	0.21	*
GM_PA	rCBF	133	1.28	173.78	1.63	*	183.82	2.37	*	130.47	1.33	160.46	1.61	*	183.77	2.33	*
	rCBV	9.82	0.1	11.6	0.11	*	13.37	0.16	*	9.15	0.08	10.91	0.11	*	13.53	0.15	*
GM_OC	rCBF	120.02	1.19	188.24	2.14	*	143.88	2.2	*	115.36	1.13	189.53	2.2	*	146.65	2.22	*
	rCBV	9.23	0.09	13.11	0.15	*	12.93	0.17	*	8.98	0.09	12.75	0.14	*	13.15	0.2	*

*Significant ($p \leq 0.05$). Data are given as mean ± SEM.

3.1. Regional CBF (rCBF)

In contrast to nitrous oxide sevoflurane increased rCBF in all regions (Table 3).

Sevoflurane increased rCBF in striatal and thalamic gray matter more than did nitrous oxide, which even decreased rCBF in right thalamic gray matter. Supratentorially, sevoflurane increased white matter and occipital rCBF more than did nitrous oxide. In contrast, in parietal and left hemispheric frontal gray matter nitrous oxide increased rCBF more than did sevoflurane (Table 4) (Figs. 3 and 4).

3.2. Regional CBV (rCBV)

Both inhalational agents increased rCBV (Table 3).

Nitrous oxide increased rCBV more than did sevoflurane in all regions except in white matter, occipital and left thalamic gray matter (Table 4) (Figs. 5 and 6).

4. Discussion

Sevoflurane increased rCBF in all regions except in parietal and frontal gray matter more than did nitrous oxide,

Table 4
Absolute change in regional cerebral blood flow (d-rCBF) [mL/100 g/min] and absolute change in regional cerebral blood volume (d-rCBV) [mL/100 g] in white matter (WM) and in grey matter (striatum (GM_ST), thalamus (GM_TH), frontal (GM_FR), parietal (GM_PA), occipital (GM_OC)) during administration of sevoflurane (0.4 MAC) (FiO2 = 0.5) (n = 9) and of nitrous oxide (0.4 MAC) (FiO2 = 0.5) (n = 9)

		Right Hemisphere			Left Hemisphere		
		Sevoflurane Mean	Nitrous oxide Mean	p	Sevoflurane Mean	Nitrous oxide Mean	p
WM	d-rCBF	18.93	2.47	*	21.31	1.66	*
	d-rCBV	0.60	0.32	*	0.69	0.06	*
GM_ST	d-rCBF	57.87	16.93	*	52.14	3.09	*
	d-rCBV	2.14	3.39	*	1.93	2.63	*
GM_TH	d-rCBF	38.93	−12.01	*	43.83	−0.34	*
	d-rCBV	0.78	1.45	*	1.44	1.87	n.s.
GM_FR	d-rCBF	37.35	31.10	*	39.47	53.26	*
	d-rCBV	0.89	4.10	*	1.27	4.92	*
GM_PA	d-rCBF	40.78	50.82	*	29.99	53.30	*
	d-r-CBV	1.78	3.55	*	1.76	4.38	*
GM_OC	d-rCBF	68.22	23.86	*	74.17	31.29	*
	d-rCBV	3.88	3.70	n.s.	3.77	4.17	n.s.

*Significant ($p \leq 0.05$). Data are given as mean.

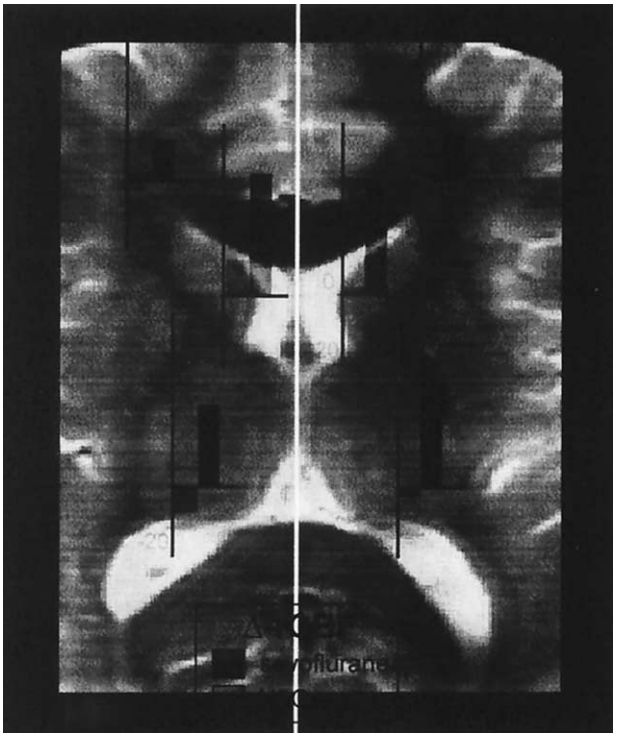

Fig. 3. Shows absolute changes in regional cerebral blood flow (**d-rCBF**) [mL/100g/min] in striatal and thalamic gray matter and in white matter during administration of sevoflurane (0.4 MAC) or nitrous oxide (0.4 MAC).

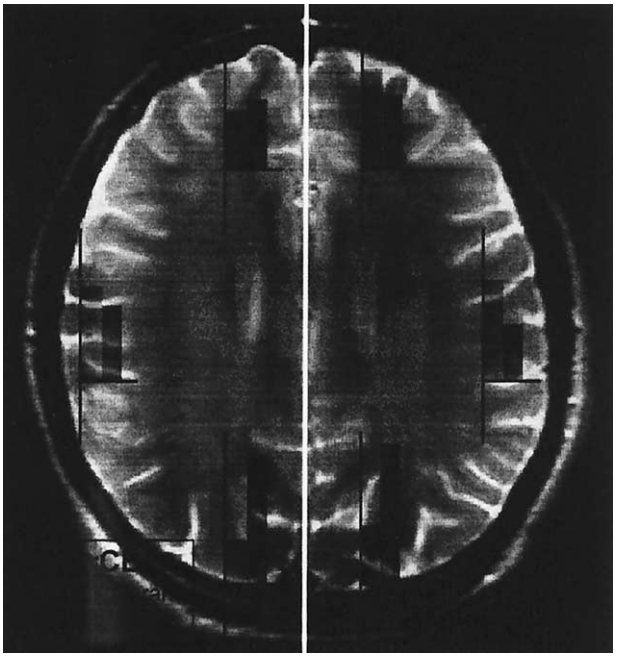

Fig. 4. Shows absolute changes in regional cerebral blood flow (**d-rCBF**) [mL/100g/min] in frontal, parietal and occipital gray matter during administration of sevoflurane (0.4 MAC) or nitrous oxide (0.4 MAC).

which, in contrast, increased rCBV in most of the gray matter regions more than did sevoflurane.

For the normal resting state an anterior-posterior gradient in rCBF was reported in humans [12] which is reversed during coma [13], sleep [14] and anesthesia [15]. Similarly, in the present study sevoflurane reversed the anterior-posterior gradient in rCBF, increasing occipital rCBF significantly more than frontal rCBF. During sevoflurane relaxation and fatigue additional to a loss of sense of time and space were reported by our volunteers, from which we assume that the observed reversal of the anterior-posterior gradient in rCBF is typical for a state of impaired consciousness preceding anesthesia in humans. Accordingly, definitive loss of consciousness during sevoflurane inhalation in humans was reported for concentrations exceeding 0.4 MAC [16].

In the present study a loss of sense of time and space was also reported for nitrous oxide although a disinhibited behavior (e.g., laughter, giggling) and the "very focused" but "not self-controlled mental activity" predominated. A loss of consciousness in humans during nitrous oxide inhalation occurs at concentrations much higher (0.65 MAC) [17] than that applied in the present study (0.4 MAC). Therefore, it is not very surprising that nitrous oxide did not reverse the anterior-posterior gradient in rCBF, as N2O increased rCBF most in frontal and parietal gray matter regions. A similar hyperfrontality of rCBF was already previously reported for nitrous oxide [18].

Nevertheless, further research is necessary to establish a relationship between a drug-specific pattern of rCBF changes and a drug-specific altered level of consciousness in humans.

Sevoflurane increased rCBF in subcortical regions (e.g., thalamic and striatal gray matter) more than did nitrous oxide, which even decreased right hemispheric thalamic rCBF. A similar redistribution of rCBF to subcortical regions was previously reported during isoflurane administration in humans [19] and in animals [20].

Both sevoflurane [3] and nitrous oxide [4] are known cerebrovasodilatators in humans. Therefore, it is of little surprise that the two drugs increased rCBV. In the nitrous oxide group, however, a relatively greater increase in rCBV than in rCBF was found, which was in contrast to the sevoflurane group.

It is a clear limitation of the present study that metabolic data during inhalation of sevoflurane or nitrous oxide (e.g., by means of phosphate spectroscopy) were not obtainable with the employed whole-body MR scanner (Magnetom VISION, Siemens, Germany). It is assumable, however, that the observed drug-specific changes in rCBF and rCBV are sum effects of drug-specific direct vascular effects and metabolically mediated vascular effects.

From the literature it is known that anesthetic doses of sevoflurane (e.g., 0.88 MAC [21]) decrease CBF and CMRO2 in humans, which is in good accordance with a relative predominance of metabolism CBF coupling-mediated vasoconstriction. In contrast, at 1.2 MAC [22] and 1.3 MAC [23] sevoflurane increased CBF in anesthetized humans. The most likely explanation therefor is an impairment

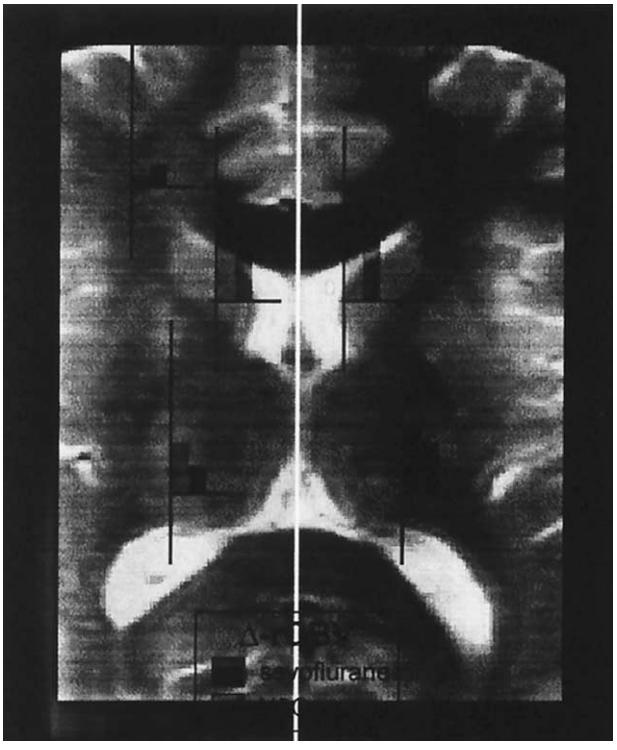

Fig. 5. Shows absolute changes in regional cerebral blood volume (**d-rCBV**) [mL/100g] in striatal and thalamic gray matter and in white matter during administration of sevoflurane (0.4 MAC) or nitrous oxide (0.4 MAC).

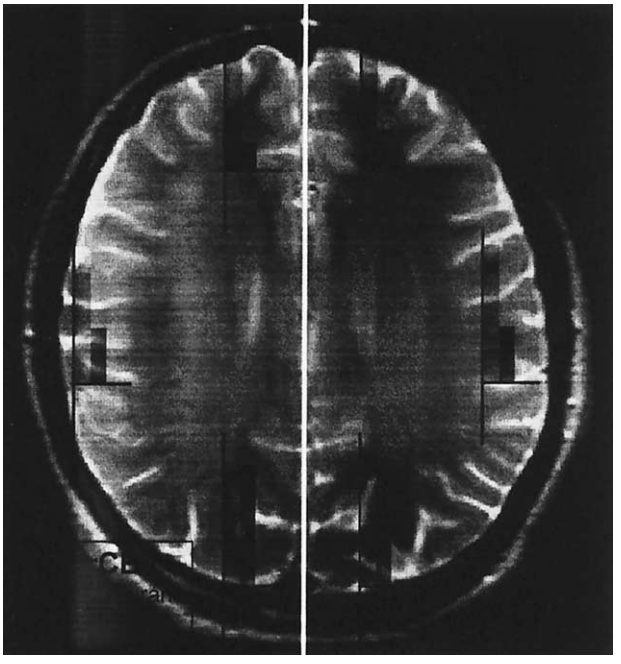

Fig. 6. Shows absolute changes in regional cerebral blood volume (**d-rCBV**) [mL/100g] in frontal, parietal and occipital gray matter during administration of sevoflurane (0.4 MAC) or nitrous oxide (0.4 MAC).

of metabolism CBF coupling, which indeed was reported to occur in humans at such doses of sevoflurane [24].

Nitrous oxide at concentrations higher than 0.65 MAC causes objective unconsciousness in humans [17]. In contrast to sevoflurane, increasing doses of nitrous oxide increase cerebral metabolism and CBF [4,20,25–27].

In order to quantify absolute CBF and CBV values by using contrast-enhanced MRI perfusion measurement, the concentration of the paramagnetic contrast agent in an arterial vessel, the arterial input function (AIF), needs to be determined. Any underestimation of AIF leads to an overestimation of CBF and CBV values. As AIF is taken in the region of the middle cerebral artery, which is a rather small vessel, it can be underestimated due to partial volume. Moreover, the assumption of a linear [7,28] instead of a non-linear [29,30] relationship between blood concentration of paramagnetic contrast agent and the susceptibility contrast can cause the AIF to be underestimated. In the present study part of the underestimation of AIF and hence overestimation of CBV and CBF was compensated for by using an improved AIF gamma variate fit [31].

Nevertheless, the present study's rCBF and rCBV values (see Table 3) are markedly higher than previously reported white (*WM*) and gray (*GM*) matter CBF and CBV values (e.g., Leenders et al.: *WM CBF*: 22.2 ± 4.9 mL/100 mL/min; *WMCBV*: 2.7 ± 0.6 mL/100 mL; *GMCBF*: 55 mL/100 mL/min; *GM CBV*: 5.2 mL/100 mL [32]), (e.g., Rempp et al.: *WMCBF*: 33.6 ± 11.5 mL/100 g/min; *WMCBV*: 4.2 ± 0.9 mL/100g; *GMCBF*: 69.7 ± 29.7 mL/100g/min; *GMCBV*: 8.0 ± 3.1 mL/100g [33]), (e.g., Frackowiak et al.: *GMCBF*: 65.3 ± 11 mL/100 mL/min, *WMCBF*: 21.4 ± 9 mL/100 mL/min [34]), which deserves explanation. The present study used gradient-echo echo-planar (GE-EPI) imaging. In contrast to spin-echo echo-planar (SE-EPI) imaging, GE-EPI imaging combines the advantages of better coverage of the brain, of being sensitive to the entire vascular bed and of a lower contrast dose [35]. Furthermore, in a very recent study Simonsen-CZ et al. reported a conversion factor (0.43) relating GE-EPI CBF and CBV values to absolute CBF and CBV values obtained with positron emission tomography (PET) [35]. Applying this conversion factor (0.43) to the present study's rCBF and rCBV values (see Table 3) yields absolute CBF and CBV values similar to those established in decades of literature. Furthermore, in the present study the ratios of CBF and CBV between gray matter and white matter were comparable to previously published gray: white matter ratios [8]. Hence changes in rCBF and rCBV e.g., during sevoflurane (0.4 MAC) or nitrous oxide (0.4 MAC) should in any case be reliably detected.

When comparing the effects of inhalational anesthetics on cerebral hemodynamics the potential influence of cerebral autoregulation and changes in paCO2 on data measurement must be considered. Cerebral autoregulation in humans has been shown to be maintained during administration of sevoflurane [22,36,37] but impaired during nitrous oxide [38]. Neither heart rate nor MAP were significantly affected by sevoflurane or nitrous oxide inha-

lation, however, meaning it is unlikely that activation of cerebral autoregulation led to the observed changes in cerebral hemodynamics.

Cerebrovascular reactivity to changes in paCO2 is also maintained during sevoflurane [21,22] and nitrous oxide [39] administration. Stable normocapnia was meticulously controlled by EtCO2 in the present study, which correlates well with paCO2 [40]. Thus, it is unlikely that paCO2-induced cerebral vasodilatation or vasoconstriction influenced rCBF or rCBV measurements during sevoflurane or nitrous oxide inhalation.

In summary we show that, in contrast to nitrous oxide, sevoflurane supratentorially reversed the anterior-posterior gradient in rCBF and redistributed rCBF to infratentorial gray matter. In contrast, nitrous oxide increased rCBV in most of the gray matter regions more than did sevoflurane. Both inhalational anesthetics had a drug-specific influence on cerebral hemodynamics, which is of importance when interpreting MRI studies of cerebral hemodynamics in anesthetized patients.

Acknowledgments

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