

Effects of Xenon Anesthesia on Cerebral Blood Flow in Humans

A Positron Emission Tomography Study

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Background: Animal studies have demonstrated a strong neuroprotective property of xenon. Its usefulness in patients with cerebral pathology could be compromised by deleterious effects on regional cerebral blood flow (rCBF).

Methods: ^{15}O -labeled water was used to determine rCBF in nine healthy male subjects at baseline and during 1 minimum alveolar concentration (MAC) of xenon (63%). Anesthesia was based solely on xenon. Absolute changes in rCBF were quantified using region-of-interest analysis and voxel-based analysis.

Results: Mean arterial blood pressure and arterial partial pressure for carbon dioxide remained unchanged. The mean (\pm SD) xenon concentration during anesthesia was $65.2 \pm 2.3\%$. Xenon anesthesia decreased absolute rCBF by $34.7 \pm 9.8\%$ in the cerebellum ($P < 0.001$), by $22.8 \pm 10.4\%$ in the thalamus ($P = 0.001$), and by $16.2 \pm 6.2\%$ in the parietal cortex ($P < 0.001$). On average, xenon anesthesia decreased absolute rCBF by $11.2 \pm 8.6\%$ in the gray matter ($P = 0.008$). A $22.1 \pm 13.6\%$ increase in rCBF was detected in the white matter ($P = 0.001$). Whole-brain voxel-based analysis revealed widespread cortical reductions and increases in rCBF in the precentral and postcentral gyri.

Conclusions: One MAC of xenon decreased rCBF in several areas studied. The greatest decreases were detected in the cerebellum, the thalamus and the cortical areas. Increases in rCBF

were observed in the white matter and in the pre- and postcentral gyri. These results are in clear contradiction with ketamine, another N-methyl-D-aspartate antagonist and neuroprotectant, which induces a general increase in cerebral blood flow at anesthetic concentrations.

THE noble gas xenon has anesthetic capacity. Although xenon has been used in clinical anesthesia since the 1950s,¹ it has not become routinely used because of its rarity and high price. However, many unique beneficial properties of xenon (e.g., neuroprotection, cardiovascular stability, no detrimental environmental effects) make it a fascinating choice for a future anesthetic.²⁻⁵ Xenon is thought to exert its anesthetic effects through N-methyl-D-aspartate receptor antagonism.⁶ This may also be the mechanism for xenon-induced neuroprotection. Although xenon may induce beneficial effects on the cellular level, its usefulness for neurosurgical patients could be compromised by nonoptimal or even harmful effects on cerebral blood flow (CBF) and metabolism. For example, ketamine, another N-methyl-D-aspartate receptor antagonist possessing neuroprotective effects, has a propensity to increase cerebral glucose metabolism and particularly CBF.⁷ Because such changes could be considered undesirable for a neurosurgical patient, assessment of the CBF effects of xenon anesthesia is of vital importance.

Previous studies assessing the effects of xenon on regional CBF (rCBF) have presented conflicting results. Some studies have reported that xenon increases rCBF,^{8,9} whereas others imply the opposite.^{10,11} Most of the data are based on animal studies in which xenon is combined with other volatile or intravenous anesthetics. To our knowledge, there are no studies assessing the effects of xenon monoanesthesia on rCBF in humans.

The aim of this study was to quantify with positron emission tomography (PET) imaging the effects of 1 minimum alveolar concentration (MAC) xenon anesthesia on rCBF under highly standardized conditions.

Materials and Methods

Subjects and Study Design

The study protocol was approved by the Ethical Committee of the Hospital District of Southwest Finland (Turku, Finland). After giving written informed consent, nine healthy, right-handed, nonsmoking volunteers aged

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20–27 yr with body mass index of 24.8 ± 2.6 kg/m² (mean \pm SD, hereinafter presented similarly) were recruited in this open, nonrandomized study. The subjects underwent a thorough physical examination and laboratory testing, including 12-lead electrocardiography. All subjects confirmed having no history of drug allergies or drug abuse, and none had ongoing medications. Magnetic resonance images (1.5-T scanner, Philips Intera system; Philips Medical Systems, Best, The Netherlands) were obtained from each subject in a separate session to exclude structural abnormalities of the brain. Subjects fasted overnight and restrained from using alcohol or any medication for 48 h before anesthesia.

¹⁵O-labeled water was used as a PET tracer to determine rCBF. PET assessment was first performed with the subjects awake to determine baseline rCBF while subjects were breathing room air. The baseline values for vital parameters were determined as mean values during the awake PET assessment. After 1 h of denitrogenation with 100% oxygen, subjects were anesthetized with xenon (Xenon Pro Anesthesia; Air Liquide Deutschland GmbH, Krefeld, Germany). The second rCBF measurement was assessed during approximately 1 MAC anesthesia. After the scan, xenon was discontinued and the subjects were allowed to recover.

Monitoring

No premedication was given. A peripheral vein was cannulated for the administration of ¹⁵O-labeled water and 0.9% saline infusion (100 ml/h). A radial artery cannula was placed during local anesthesia for blood sampling and invasive blood pressure monitoring. Ventilation parameters, breathing gases (oxygen, carbon dioxide, xenon), and airway pressures were monitored throughout the anesthesia. Vital parameters and depth of hypnosis were monitored using a GE Datex-Ohmeda S/5 anesthesia monitor (GE Healthcare, Helsinki, Finland) with plug-in modules recording continuously noninvasive and invasive blood pressures, five-lead electrocardiography, pulse oximetry (E-PRESTIN Module; GE Healthcare), Bispectral Index (E-BIS Module; GE Healthcare; algorithm version 4.0, XP-level), and nasopharyngeal temperature. A portable computer running S/5 Collect software (GE Healthcare) was used for data recording. Arterial blood samples were obtained during scanning, and hematocrit and partial pressures of oxygen and carbon dioxide were repeatedly analyzed with portable equipment (*i*-STAT; Abbott Laboratories, Birmingham, United Kingdom).

Anesthesia

To enable 63% xenon (the estimated MAC value for xenon)¹² in the closed-system ventilation, the partial pressure of nitrogen solved in the tissues must be considerably decreased. Denitrogenation was performed with subjects breathing spontaneously 100% oxygen

through 5 cm H₂O continuous positive airway pressure mask for 1 h before the induction. End-tidal oxygen concentration was allowed to reach 92% before xenon administration. Thereafter, the induction was performed by changing the inhaled oxygen concentration from 100% to 21%, thus letting the xenon concentration in the gas mixture to increase. Induction was facilitated by several flushes to gain the target concentration of 63% xenon. During the induction, the subjects breathed xenon spontaneously through a tightly fitting facemask, and they were repeatedly requested to squeeze the investigator's hand twice. Failure to comply with the request was interpreted as loss of consciousness. A PhysioFlex closed-system ventilator (Dräger, Lübeck, Germany) was used for mask induction and for mechanical ventilation during the maintenance of anesthesia.¹³ After the loss of consciousness, a 0.8-mg/kg bolus of rocuronium (Esmeron, 10 mg/ml; Organon, Helsinki, Finland) was administered for muscle relaxation, and the subjects were endotracheally intubated. Anesthesia was maintained with xenon as a single anesthetic, and additional doses of rocuronium were given to maintain relaxation at one twitch of train-of-four. In case of definite pain reaction due to intubation (rapid increase in blood pressure and heart rate), subjects were given a single 25- μ g intravenous dose of remifentanyl (Ultiva; Glaxo-SmithKline, Espoo, Finland) immediately after the induction. Ventilation was adjusted to maintain the arterial blood partial pressure of carbon dioxide at baseline level, and the BairHugger warming system (Arizant Healthcare Inc., Eden Prairie, MN) was used to stabilize body temperature. After the induction, a 30-min minimum stabilization period was allowed to pass before the second PET scan. After completing the scan, xenon was discontinued and muscle relaxation was reversed with a neostigmine-glycopyrrolate combination (Robinul Neostigmin; Wyeth Lederle, Vantaa, Finland). Subjects were extubated as they recovered spontaneous breathing and regained consciousness. They were monitored for stable vital signs for a minimum of 1 h. The subjects were discharged according to our hospital's standard criteria for ambulatory surgery patients.

PET Assessment

The PET scans were performed with a GE Advance PET Scanner (GE Medical System, Milwaukee, WI), and ¹⁵O-labeled water was used as a tracer, as described in detail previously.¹⁴ rCBF was assessed at baseline (awake) and during 1 MAC xenon anesthesia. Scans were performed in a dim room, and sudden loud noises were avoided. Positioning of the head was done using anatomical landmarks and laser alignment lights. Automated infusion equipment was used to administer a 300-MBq intravenous bolus of H₂¹⁵O within 15 s followed by 90-s static three-dimensional tissue activity image acquisition. A roller pump and two-channel detector device were used

for detection of arterial blood activity as previously described.¹⁴

Data Analysis

Preprocessing of PET Data. The preprocessing of imaging data were performed using the Statistical Parametric Mapping¹⁵ software version 99 (SPM99) and Matlab 6.5 for Windows (Math Works, Natick, MA) with a previously described procedure.¹⁴ Briefly, parametric images of rCBF were calculated from the tracer activity images and plasma activity curves using tracer kinetic modeling as described in our previous article.¹⁴ Each subject's images were realigned (motion correction). The normalization parameters for each subject were estimated from the mean image using a default algorithm and a ¹⁵O-water PET template delivered with SPM99.

Automated ROI Analysis. To quantify rCBF, an automated region-of-interest (ROI) analysis^{16,17} was performed using standardized ROIs defined on magnetic resonance template image representing brain anatomy in accordance with the Montreal Neurologic Institute (MNI) space database. Because this method is based on common stereotactic space, *i.e.*, spatial normalization of images, the operator-induced error in defining ROIs individually for each subject can be avoided. The ROIs were defined using Imadeus (version 1.20; Forima Inc., Turku, Finland) bilaterally on the frontal (19 planes), parietal (9 planes), medial temporal (9 planes), lateral temporal (10 planes), and occipital (7 planes) cortices; the anterior (10 planes) and posterior (6 planes) cingulate cortices; the insular cortex (8 planes); the thalamus (6 planes); the caudate (8 planes); the putamen (7 planes); the cerebellum (6 planes); and the white matter (5 planes). The average rCBF values were calculated from spatially normalized rCBF images. The average gray matter value was calculated using individual gray matter ROIs.

Voxel-based Image Analysis. Voxel-based statistical image analysis was performed with SPM99 as described previously.¹⁴ Within-subject subtraction analysis with T contrasts was used to test xenon-induced changes in rCBF between the conditions. Because rCBF values of parametric images are quantitative, SPM analyses were performed without global normalization, *i.e.*, using absolute rCBF values. The analysis was performed as an exploratory analysis covering the whole brain, *i.e.*, without any *a priori* hypothesis or spatial constrictions regarding the location of possible differences. A *P* value less than 0.05 (corrected for multiple comparisons) was considered statistically significant. The visualizations were performed with a height threshold *T* value of at

Table 1. Summary of Vital Parameters at Awake and 1 MAC Xenon Anesthesia

Parameter	Awake	1 MAC Xenon	<i>P</i> Value
Xenon concentration, %	—	65.2 ± 2.3	NA
Mean arterial pressure, mmHg	91.1 ± 5.4	91.4 ± 8.5	NS
Heart rate, beats/min	60.1 ± 7.9	55.7 ± 8.9	0.02
Peripheral oxygen saturation, %	98.3 ± 0.6	96.3 ± 2.1	0.005
End-tidal CO ₂ , mmHg	42.0 ± 2.3	39.0 ± 3.0	0.001
Arterial Pco ₂ , mmHg	41.3 ± 2.3	41.3 ± 3.8	NS
Arterial Po ₂ , mmHg	92.1 ± 7.7	87.2 ± 11.0	NS
Hematocrit, %	43.1 ± 1.9	42.9 ± 1.5	NS
Temperature, °C	36.4 ± 0.2	36.0 ± 0.3	0.017
Respiratory rate, breaths/min	12.6 ± 2.6	9.9 ± 1.5	0.010

Values are group mean ± SD.

CO₂ = carbon dioxide; MAC = minimum alveolar concentration; NA = not applicable; NS = not significant; Pco₂ = partial pressure of carbon dioxide; Po₂ = partial pressure of oxygen.

least 3.0. The nonsignificant clusters were discarded from the visualizations by adjusting the minimum cluster size (extend threshold, *k*). The localization of the results of the SPM analysis was made using the MNI Space utility, `##` which first converts the MNI coordinates given by SPM to Talairach coordinates using nonlinear transformation^{18***} and then identifies each voxel by the anatomical labels presented in the Talairach Daemon database.¹⁹

Statistical Analysis of ROI and Monitoring Data. All enrolled subjects were included in the statistical analyses. Quantitative rCBF and vital monitoring variables were analyzed with repeated-measures analysis of variance model having the condition (baseline and during anesthesia) as a within factor. The robustness of the statistical analysis was checked by replicating the analysis with nonparametric methods, *i.e.*, with Wilcoxon signed rank test. To study the effect of remifentanyl, another repeated-measures analysis of variance model was fitted, including the condition as a within factor and the use of remifentanyl (no/yes) as a between factor. The pairwise comparisons were performed using the linear contrasts of the same model. A two-sided *P* value of less than 0.05 was considered statistically significant. Statistical analyses were conducted with SAS (version 8.2; SAS Institute Inc., Cary, NC) by 4Pharma Ltd. (Turku, Finland).

Results

A summary of vital parameters is presented in table 1. The mean xenon concentration (± SD) during anesthesia was 65.2 ± 2.3%. The arterial partial pressure for carbon dioxide and the mean blood pressure and hematocrit remained unchanged between the scans. Peripheral oxygen saturation decreased by 2.0% (*P* = 0.005) and body temperature decreased by 0.9% (*P* = 0.02) during xenon anesthesia. The mean partial pressure for

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Table 2. Absolute Regional Cerebral Blood Flow ($\text{ml} \cdot 100 \text{g}^{-1} \cdot \text{min}^{-1}$) Values of Region of Interest–defined Structures

Region	Awake	1 MAC Xenon	P Value
Frontal cortex	49.28 \pm 8.12	41.67 \pm 6.40	<0.001
Medial temporal cortex	40.22 \pm 7.08	38.00 \pm 7.10	NS
Lateral temporal cortex	46.53 \pm 7.95	44.70 \pm 6.90	NS
Occipital cortex	42.06 \pm 8.66	43.26 \pm 6.05	NS
Parietal cortex	48.54 \pm 8.62	40.50 \pm 6.35	<0.001
Insula	58.48 \pm 10.24	57.85 \pm 9.09	NS
Anterior cingulate	59.36 \pm 14.96	56.94 \pm 9.62	NS
Posterior cingulate	53.50 \pm 10.13	46.50 \pm 7.91	0.008
Caudate	52.47 \pm 11.22	48.61 \pm 8.58	NS
Putamen	58.80 \pm 10.39	57.60 \pm 6.76	NS
Thalamus	58.62 \pm 10.87	44.61 \pm 6.11	0.001
Cerebellum	51.70 \pm 8.10	33.75 \pm 7.32	<0.001
White matter	15.87 \pm 2.49	19.39 \pm 3.69	0.001

Values are group mean \pm SD.

MAC = minimum alveolar concentration; NS = not significant.

arterial oxygen was 92.1 ± 7.7 at baseline and 87.2 ± 11.0 mmHg during anesthesia (not significant). The mean value for the Bispectral Index was 94.9 ± 2.2 with the subjects awake and 24.8 ± 5.0 during the second PET scan ($P < 0.001$). Five subjects (55%) received a single bolus dose of $25 \mu\text{g}$ remifentanyl (mean dose, $0.30 \mu\text{g}/\text{kg}$) during intubation because of a clinically evident pain reaction. The mean time interval between opioid bolus and the second PET scan was 34 min (range, 30–39 min).

Automated ROI Analysis

The baseline values for rCBF in the ROIs were 15.9 – $59.4 \text{ ml} \cdot 100 \text{g}^{-1} \cdot \text{min}^{-1}$. The absolute CBF values for each individual region are presented in table 2. rCBF changes individually in the thalamus, the cortical areas, and the insula are presented in figure 1. rCBF decreased by $34.7 \pm 9.8\%$ in the cerebellum ($P < 0.001$), by $22.8 \pm 10.4\%$ in the thalamus ($P = 0.001$), by $16.2 \pm 6.2\%$ in the parietal cortex ($P < 0.001$), by $15.1 \pm 7.3\%$ in the

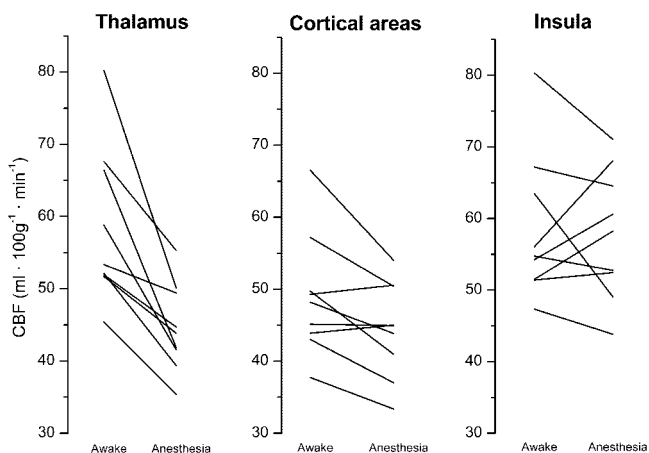


Fig. 1. Individual changes in regional cerebral blood flow (CBF) in the thalamus, the cortical areas, and the insula from baseline (awake) to 1 minimum alveolar concentration of xenon.

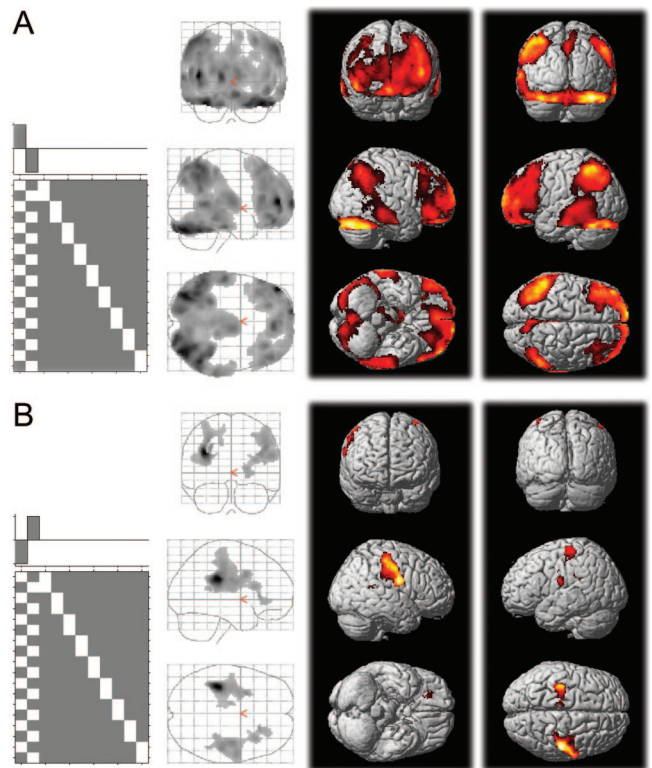


Fig. 2. Regions of statistically significant decreases (A) and increases (B) in absolute regional cerebral blood flow in voxel-based analysis. The height threshold (T) was set to 3.0, and the extend threshold (k) was set to 500 (A) and 1,000 (B). See Materials and Methods, Data Analysis, Voxel-based Image Analysis for details. The stereotactic coordinates are presented in tables 1 and 2 on the ANESTHESIOLOGY Web site.

frontal cortex ($P < 0.001$), and by $12.5 \pm 8.9\%$ in the posterior cingulate ($P = 0.008$). rCBF increased in the white matter by $22.1 \pm 13.6\%$ ($P = 0.001$). On average, in the cortical regions the mean rCBF decreased by $8.7 \pm 8.3\%$ ($P = 0.020$). In all gray matter regions (cortical regions and the deep nuclei), the mean rCBF decreased by $11.2 \pm 8.6\%$ ($P = 0.008$). Remifentanyl did not affect rCBF changes in any of the brain regions studied.

SPM Analysis

Xenon anesthesia caused statistically significant reduction in the absolute CBF in the frontal, temporal, parietal, and occipital lobes. The clusters representing the CBF decrease extended also to the limbic lobe, the cerebellum, the thalamus, the brain stem, and the lentiform nucleus. Absolute CBF increases were detected bilaterally in the precentral and postcentral gyri. The increases and decreases are shown in figures 2A and B. Additional information regarding this is available on the ANESTHESIOLOGY Web site at www.anesthesiology.org.

Discussion

One minimum alveolar concentration xenon anesthesia decreased rCBF from awake baseline in several brain

areas. Greatest reductions were observed in the cerebellum, the thalamus, and the cortical areas. rCBF increased in the white matter. Furthermore, SPM analysis revealed increases in the precentral and postcentral gyri.

Previous animal studies on the CBF effects of xenon have been controversial. Autoradiography study with rats and sagittal sinus outflow study with pigs showed no change in rCBF during steady state inhalation of xenon.^{11,20} However, one study using radiolabeled microspheres in pigs demonstrated a 38% increase in cortical CBF during xenon anesthesia.²¹ In monkeys, subanesthetic xenon caused a global reduction in CBF,¹⁰ whereas anesthetic concentration (80%) increased absolute CBF by 53%.²² Although both of these studies with primates used the sagittal sinus microelectrodes method, the latter was compromised with significant variation in the partial pressure for carbon dioxide (35–46 mmHg). Interestingly, an increase in rCBF has been observed during first few minutes of xenon inhalation in rats but not during steady state anesthesia.²⁰

To our knowledge, there are no previous PET studies on the rCBF effects of xenon anesthesia in humans. However, few studies have been performed with other methodology. Using xenon-133 clearance, subanesthetic (35%) xenon was shown to increase human rCBF by approximately 12%.²³ Furthermore, significantly increased middle cerebral artery flow velocities were observed in humans breathing anesthetic (65%) xenon.²⁴ The inconsistency of animal and human results may partly be explained by adjuvant anesthetic agents and by nonfixed carbon dioxide levels. It should also be pointed out that interspecies differences in the MAC value for xenon should be taken into consideration when comparing animal and human data.^{8,12,25}

In the current study, the physiologic variables known to affect cerebral perfusion were carefully standardized. There were no significant changes detected in the partial pressure for arterial carbon dioxide or hematocrit. Also, the mean arterial pressure maintained unchanged and well within the range of intact cerebral autoregulation during the study. Previously, it has been demonstrated with pigs that cerebral autoregulation remains intact during xenon anesthesia.¹¹ It has been shown that cerebral metabolic rate of oxygen decreases 5–6% per 1°C.²⁶ Because the mean decrease in absolute body temperature was only 0.34°C in the current study, the concomitant changes in CBF can be considered minor. There was a minor decrease in peripheral oxygen saturation as well as in partial pressure for arterial oxygen during xenon anesthesia. The measured values for arterial oxygen were, however, notably higher than values known to increase cerebral blood flow.²⁷

In the current study, the target level for xenon was 1 MAC (63% xenon),¹² instead of aiming at a particular depth of hypnosis. Anesthetic depth monitors, *e.g.*, Bispectral Index, have not been validated for xenon

anesthesia, and their usefulness has even been questioned during the emergence from xenon anesthesia.²⁸ The actual mean xenon concentration was 65.2%, which was quite close to the target. During steady state anesthesia, the Bispectral Index was remarkably low in all subjects, suggesting adequate depth of anesthesia. In the questionnaire, none of the subjects reported awareness during anesthesia.

To attenuate the pain reaction induced by intubation, five subjects received a bolus of short-acting opioid, remifentanyl. Remifentanyl has been shown to induce changes in rCBF *per se*.²⁹ On the other hand, major pain responses could cause even more considerable changes in rCBF. Considering the mean time interval between the opioid bolus and the second rCBF assessments and the extremely short half-life of remifentanyl (approximately 3 min in healthy young men³⁰), it is unlikely that it would have affected the results. This possibility was taken into consideration in the statistical analysis and, importantly, remifentanyl did not affect the CBF results.

In physiologic circumstances, changes in rCBF parallel changes in regional cerebral glucose metabolism, which should, ultimately, reflect alterations in neuronal activity. Assuming that coupling is preserved during xenon anesthesia, the observed reduction in rCBF could represent decreased metabolism. In a recent study, it was shown that surgical concentrations of xenon induce a global reduction in regional cerebral glucose metabolism in humans.³¹ Interestingly, another *N*-methyl-D-aspartate antagonist, *S*-ketamine, was previously shown to increase rCBF, but in excess of metabolic needs in anesthetic concentrations.⁷ It is known that general anesthetics can induce vasodilatation in the cerebral vasculature, potentially leading to an imbalance in the relation between CBF and metabolism.^{7,14,32–35} A more fundamental evaluation of the flow–metabolism relation during xenon anesthesia would require concomitant assessment of rCBF and brain metabolism. Concomitant measurement of oxygen consumption using the gaseous PET tracer ¹⁵O-labeled oxygen was not technically possible in the current study because of the applied closed-system ventilation.

SPM analysis revealed bilateral rCBF increases in the precentral and postcentral gyri. The implication of this deviant finding can only be speculated. Assuming intact flow–metabolism coupling, this could reflect neuronal activation in these areas receiving somatosensory information. Xenon monoanesthesia may not be sufficient to suppress all responses to the noxious stimulus in the current study, *i.e.*, the intubation tube. Concomitant assessment of glucose consumption using ¹⁸F-labeled fluorodeoxyglucose would be needed to resolve whether neuronal activation is involved.

There are also other limitations related to measuring only rCBF. Small changes in vessel diameter can cause considerable changes in CBF, and changes in CBF and

cerebral blood volume do not always parallel each other, especially in the injured brain.³⁶ Assessment of cerebral blood volume using ¹⁵O-labeled carbon monoxide would have been warranted but was, for technical reasons already explained (gaseous PET tracer), not possible in the current study. Furthermore, the impact and relevance of CBF and cerebral blood volume changes on intracranial pressure can only be assessed in patients with decreased intracranial compliance.

The relevance of the increase in the white matter also remains speculative. It is unlikely that metabolic needs in the white matter would be increased. Our results suggest, however, that xenon anesthesia induces changes in blood flow distribution in the brain, *i.e.*, a decrease in the gray matter and an increase in the white matter. This could be due to direct vasodilatory effects of the drug.³⁷ The vasodilatory effect in the gray matter could be overridden by reduced CBF coupled to decreased metabolism as a consequence of xenon's anesthetic effects. Nevertheless, the effects of anesthetics on blood flow and metabolism in the gray matter are far better known than in the white matter.

In conclusion, xenon anesthesia decreased rCBF especially in the cerebellum, the thalamus, and cortical areas. rCBF increased in the white matter and in parts of the precentral and postcentral gyri. These results are in clear contradiction with ketamine, another *N*-methyl-*D*-aspartate antagonist and neuroprotectant, which induces a general increase in CBF at anesthetic concentrations.

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