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# S-Ketamine Anesthesia Increases Cerebral Blood Flow in Excess of the Metabolic Needs in Humans

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***Background:*** **Animal studies have demonstrated neuroprotective properties of *S*-ketamine, but its effects on cerebral blood flow (CBF), metabolic rate of oxygen ($CMRO_2$), and glucose metabolic rate (GMR) have not been comprehensively studied in humans.**

***Methods:*** **Positron emission tomography was used to quantify CBF and $CMRO_2$ in eight healthy male volunteers awake and during *S*-ketamine infusion targeted to subanesthetic (150 ng/ml) and anesthetic (1,500–2,000 ng/ml) concentrations. In addition, subjects' GMRs were assessed awake and during anesthesia. Whole brain estimates for cerebral blood volume were obtained using kinetic modeling.**

***Results:*** **The mean ± SD serum *S*-ketamine concentration was 159 ± 21 ng/ml at the subanesthetic and 1,959 ± 442 ng/ml at the anesthetic levels. The total *S*-ketamine dose was 10.4 mg/kg. *S*-ketamine increased heart rate (maximally by 43.5%) and mean blood pressure (maximally by 27.0%) in a concentration-dependent manner ($P = 0.001$ for both). Subanesthetic *S*-ketamine increased whole brain CBF by 13.7% ($P = 0.035$). The greatest regional CBF increase was detected in the anterior cingulate (31.6%; $P = 0.010$). No changes were detected in $CMRO_2$. Anesthetic *S*-ketamine increased whole brain CBF by 36.4% ($P = 0.006$) but had no effect on whole brain $CMRO_2$ or GMR. Regionally, CBF was increased in nearly all brain structures studied (greatest increase in the insula 86.5%; $P < 0.001$), whereas $CMRO_2$ increased only in the frontal cortex (by 15.7%; $P = 0.007$) and GMR increased only in the thalamus (by 11.7%; $P = 0.010$). Cerebral blood volume was increased by 51.9% ($P = 0.011$) during anesthesia.**

***Conclusions:*** **S-ketamine–induced CBF increases exceeded the minor changes in $CMRO_2$ and GMR during anesthesia.**

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UNDERSTANDING the central nervous system effects of anesthetic regimens is essential for optimal care of patients with cerebral pathology. An ideal anesthetic would produce a safe, steady anesthesia with uniform decrease in both cerebral blood flow (CBF) and metabolism combined to neuroprotective properties.

The noncompetitive *N*-methyl-D-aspartate antagonist ketamine is an intravenously administered anesthetic agent possessing a short duration of action, a strong supporting effect on the cardiovascular system, and a moderate analgesic property. Because of these unique and potentially beneficial characteristics, ketamine has been deemed particularly suitable for anesthesia and sedation of trauma patients. In addition, ketamine has been shown to block the excitotoxic effects of glutamate *in vitro* [1] and to reduce neuronal damage in rats experiencing cerebral ischemia[2,3] or head trauma[4] *in vivo*.

Racemic ketamine has been proposed to possess many of the required characteristics for neuroanesthesiologic use.[5] Regardless of the considerable amount of variable results presented on its CBF and metabolic effects,[6–12] subanesthetic doses of sole racemic ketamine seem to principally increase human CBF and glucose metabolic rate (GMR), with only minor effects on cerebral metabolic rate of oxygen ($CMRO_2$).[13–15] However, pure anesthesia with racemic ketamine has been associated with increased whole brain CBF with no changes in either of the metabolic components ($CMRO_2$ and GMR) in humans.[16] Based on this information, at least the racemic mixture of ketamine would seem unsuitable for neuroanesthesiologic use.

The *S*-enantiomer of ketamine, however, seems more promising. In addition to not effecting cerebral autoregulation when administered during propofol anesthesia in humans,[5] *S*-ketamine possesses an even stronger neuroprotective property in animals than the racemate.[17] Although subanesthetic *S*-ketamine seems to increase cerebral GMR in humans,[18] a recently published study reported widespread GMR decreases in rats anesthetized with *S*-ketamine.[19] The effects of *S*-ketamine on CBF or $CMRO_2$ have not been studied.

The purpose of this study was to quantify the CBF and metabolic effects of subanesthetic and anesthetic *S*-ketamine, without other anesthetic agents, in healthy human brain by using positron emission tomography (PET). Because subanesthetic racemic ketamine seems to increase CBF with divergent effect on the two metabolic components (increase in GMR combined to minor effect

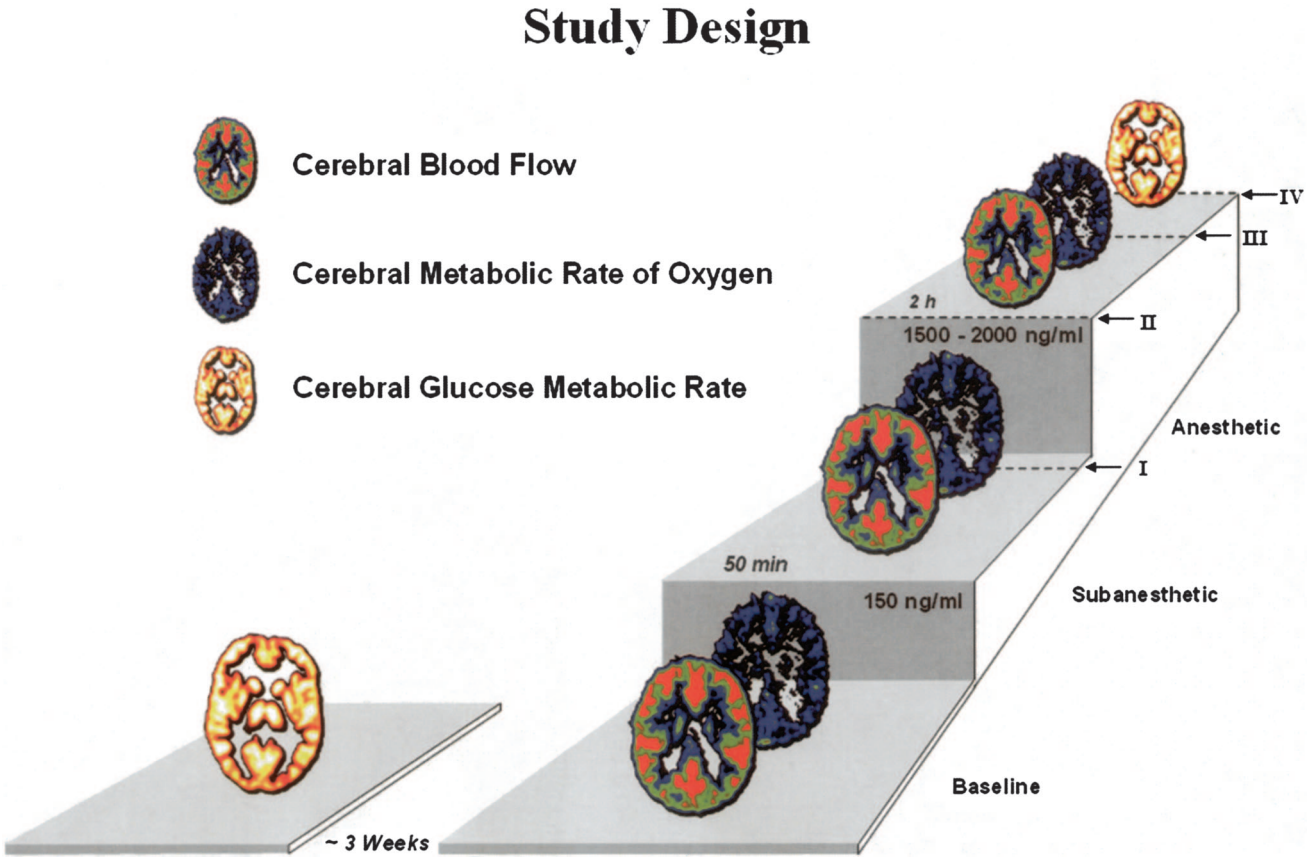


**Fig. 1. Study design showing the timing and order of the individual positron emission tomography measurements at baseline and during target-controlled *S*-ketamine infusion aiming at subanesthetic (150 ng/ml) and anesthetic (1,500–2,000 ng/ml) concentrations. The baseline measurement for cerebral glucose metabolic rate was performed approximately 3 weeks apart from the other assessments (for further details, see Materials and Methods). The mean durations of the subanesthetic and anesthetic levels were 50 min and 2 h, respectively. The *S*-ketamine serum concentration measurements are indicated with Roman numerals (*I–IV*) and corresponding *arrows*.**

on $CMRO_2$),[13,14] we wanted to assess all of these three variables within subjects during the awake state and during *S*-ketamine anesthesia.

## 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, eight healthy (American Society of Anesthesiologists physical status class I), nonsmoking, right-handed male volunteers aged 20–27 yr with body mass index of 24.1 ± 1.8 (mean ± SD) were recruited in this open, nonrandomized, dose-escalation study. All subjects underwent a detailed prestudy examination, including laboratory data and a 12-lead electrocardiogram. They confirmed having no history of mental illness, drug allergies, or drug abuse, and none had ongoing medications. The subjects refrained from using alcohol or any medication for 48 h before the scans.

$^{15}$O-labeled water and oxygen ($[^{15}O]O_2$) and $^{18}$F-labeled fluorodeoxyglucose ($[^{18}F]$FDG) were used as PET tracers to assess regional CBF (rCBF), regional $CMRO_2$ ($rCMRO_2$), and regional GMR (rGMR), respectively, at baseline (no drug) and during *S*-ketamine anesthesia. Additional assessments for rCBF and $rCMRO_2$ were performed during subanesthetic *S*-ketamine before the induction of anesthesia. Because of the long half-life of $^{18}$F (110 min), the baseline $[^{18}F]$FDG scan had to be performed on a separate day. This was scheduled approximately 3 weeks apart from the other scans to secure proper wound healing for radial artery recannulation. Subjects fasted 6 h before the baseline $[^{18}F]$FDG scan and overnight before anesthesia. The study design is presented in figure 1.

*Monitoring of the Subjects*

The left radial artery and two large veins in the right forearm were cannulated for blood sampling and for administration of 0.9% NaCl (50 ml/h), *S*-ketamine (25 mg/ml Ketanest-S; Pfizer Inc., New York, NY), $^{15}$O-labeled water, and $[^{18}F]$FDG. After the cannulations, the subjects were connected to a monitor (S/5™ Anesthesia Monitor with M-CAiOVX and M-NESTPR plug-in modules; Datex-Ohmeda Division, Instrumentarium Corp.,

General Electric Company, Helsinki, Finland) recording the electrocardiogram, noninvasive mean blood pressure, heart rate, respiratory rate, state of muscle relaxation (train-of-four), peripheral oxygen saturation, and end-tidal carbon dioxide ($ETco_2$). A portable computer running the S/5 Collect software (Datex-Ohmeda S/5 Collect Version 4.0; Datex-Ohmeda Division, Instrumentarium Corp.) was used for recording the individual values for vital signs, train-of-four, and $ETco_2$ every 30 s and mean blood pressure every 5–10 min throughout the study. The arterial blood hematocrit, gas analysis, and acid–base status were determined before each $rCMRO_2$ measurement. Subjects' $ETco_2$ values were maintained strictly at baseline level (particularly during rCBF assessments), with verbal breathing instructions during subanesthetic *S*-ketamine and with ventilator adjustments during anesthesia.

### *Administration of* S*-ketamine and Anesthetic Considerations*

No premedication was given. A Harvard 22 syringe pump (Harvard Apparatus, South Natick, MA) connected to a portable computer running Stanpump software[20]§§ was used to administer *S*-ketamine as a continuous intravenous target-controlled infusion aiming at pseudo–steady state serum drug concentrations for subanesthetic and anesthetic *S*-ketamine. The kinetic parameters for racemic ketamine[21] were used for *S*-ketamine in the current study because of marginal differences in the kinetics of the ketamine enantiomers.[22]

The target concentration level for subanesthetic *S*-ketamine was set to 150 ng/ml. A stabilization period of 18 ± 7 min was allowed to pass before the PET scans were initiated. The subanesthetic *S*-ketamine infusion lasted approximately 50 min. Anesthesia was induced with a zero-order *S*-ketamine infusion of 0.15 mg · $kg^{-1}$ · $min^{-1}$ after the PET scans at subanesthetic level had been completed. During the induction, the subjects were repeatedly requested to squeeze the investigator's hand twice. Failure to comply with the request was interpreted as loss of consciousness. During the induction, the subjects breathed 100% oxygen *via* facemask. As the subjects became clinically unresponsive, a 0.6- to 1-mg/kg intravenous dose of rocuronium (10 mg/ml Esmeron; Oy Organon Ab, Helsinki, Finland) was administered to produce muscle relaxation, and the subjects were tracheally intubated and connected to a Servo 900C ventilator (Siemens Medical Solutions, Solna, Sweden). For maintenance of anesthesia, the target concentration level of *S*-ketamine was initially set to 1,500–2,000 ng/ml based on the individual dose needed for loss of consciousness. The targeted concentration was then adjusted with ±250 ng/ml increments according to the subjects' clinical signs. Immediately after the induction, the ventilation was set to an oxygen–air mixture (30/70), 100 ml · $kg^{-1}$ · $min^{-1}$, with respiration frequency at 15 breaths/min. Ventilation was then adjusted to maintain the individual $ETco_2$ at baseline level during anesthesia. Muscle relaxation was maintained at one or two twitches of train-of-four with additional intravenous bolus doses of rocuronium (5–30 mg). After commencing the pseudo–steady state *S*-ketamine anesthesia, a stabilization period of 33 ± 2 min was allowed to pass before the PET scans were initiated. Steady state anesthesia lasted for approximately 2 h.

After the PET scans during anesthesia had been completed, the *S*-ketamine infusion was discontinued, and the subjects were given a 4-mg bolus dose of ondansetron (2 mg/ml Zofran; GlaxoSmithKline Oy, Espoo, Finland) and a 1- to 2-mg bolus dose of midazolam (1 mg/ml Dormicum; Roche Pharmaceuticals, Basel, Switzerland) intravenously. Residual muscle relaxation was reversed with a neostigmine–glycopyrrolate (Glycostigmin; Oy Leiras Finland Ab, Helsinki, Finland) combination, and the subjects were extubated as they regained consciousness. Additional intravenous bolus doses of ondansetron and midazolam were given if necessary to treat emesis and ketamine-induced hallucinations, respectively. After the anesthesia, the subjects were monitored until their vital signs had been stable for at least an hour. The local routine postanesthesia discharge criteria were applied when the subjects were allowed to leave the study premises. The next day and approximately 10 months after the anesthesia, the subjective *S*-ketamine–induced sensations and experiences were recorded, and a modified questionnaire by Brice *et al.*[23] was completed for determination of possible awareness during anesthesia.

A 5-ml arterial blood sample was collected for determination of serum *S*-ketamine concentration at the end of the subanesthetic level (sample I), at the moment subjects lost consciousness (sample II), and after the $CMRO_2$ (sample III) and GMR (sample IV) assessments during anesthesia (fig. 1). Sera of the samples were immediately separated and kept frozen at −70°C until analyzed with high-performance liquid chromatography (Yhtyneet laboratoriot, Helsinki, Finland).[24]

### *PET Assessments*

$^{15}O$-labeled water was used to assess rCBF, $[^{15}O]O_2$ to assess $rCMRO_2$ and [$^{18}$F]FDG to assess rGMR. Assessments for rCBF and $rCMRO_2$ were performed at baseline and during subanesthetic and anesthetic *S*-ketamine lasting together approximately 22 min on each level. Assessment for rGMR was performed at baseline (approximately 3 weeks apart from the other studies) and during *S*-ketamine anesthesia. rGMR scans lasted 60 min each (fig. 1).

§§ STANPUMP program. Available at: http://anesthesia.stanford.edu/pkpd. Accessed July 2, 2005.

Descriptions of tracer production and administration, image processing, and the PET scanner are given in our previous articles.[13,14,25–27] Individual magnetic resonance images were acquired for anatomical reference with a 1.5-T scanner (GE Signa Horizon LX CX; General Electric Company, Milwaukee, WI) in a separate session.

*Data Analysis*

**Quantitative Region-of-interest Analysis.** Before the region-of-interest (ROI) analysis, realignment of the PET images and the coregistration of the individual magnetic resonance images (MRI) to the PET images were performed using Statistical Parametric Mapping (SPM) software (version 99; Wellcome Department of Cognitive Neurology, University College London, London, England).[28]

The realignment parameters were first obtained by realigning the subject's consecutive summation images separately for each tracer. These parameters were then used for the realignment of the individual parametric (rCBF) or dynamic ($[^{15}O]O_2$ and [$^{18}$F]FDG) images. Because the differences in head position between the individual tracer activity acquisitions ($^{15}$O-labeled water, $[^{15}O]O_2$, and [$^{18}$F]FDG) obtained during anesthesia were considered minimal, these scans were used as reference images in the realignment. The individual [$^{18}$F]FDG mean summation image was calculated and used for the coregistration and reslicing of the individual MRIs to achieve matching image planes.

Individual ROIs were drawn to the planes of the coregistered MRIs using Imadeus 1.15 (Forima Inc., Turku, Finland) to bilaterally outline the frontal (on 11- to 12-image planes), parietal (5 planes), temporal (5 planes), and occipital (3–4 planes) gray matter; the anterior (5 planes) and posterior (2–3 planes) cingulate; the insula (3–4 planes); the thalamus (2–3 planes); the caudate (3 planes); the putamen (2–3 planes); and the cerebellum (2–3 planes). The whole brain values were determined by drawing a single ROI outlining all brain tissue inside the skull on 3 planes superior to the lateral ventricles. The ROIs were then transferred to the corresponding planes of the PET images to obtain individual values for rCBF, $rCMRO_2$, and rGMR.

The kinetic modeling for rCBF and rGMR was performed similarly to our previous studies.[14,25] To improve the accuracy of $CMRO_2$ modeling, the whole brain cerebral blood volume (CBV) was first estimated from each $[^{15}O]O_2$ acquisition by using a multilinear model for arterial and tissue (the whole brain ROI) activity. These CBV estimates were then used in the modeling for $rCMRO_2$. Otherwise, the modeling for $rCMRO_2$ was performed as described in our previous article.[26]

The oxygen extraction fraction (OEF) was determined for each brain region as described in our previous article.[26] For the calculation of the whole brain oxygen-to-glucose index (OGI), the unit conversion was first performed using the molar volume of an ideal gas (22.4 l/mol) to obtain the individual whole brain $CMRO_2$ values in $\mu mol \cdot 100\,g^{-1} \cdot min^{-1}$. These values were then divided by the whole brain GMR.

**Statistical Analysis of ROI and Monitoring Data.** Quantitative CBF, $CMRO_2$, GMR, OEF, OGI, and physiologic variables were analyzed with repeated-measures analysis of variance having the drug concentration as a within-factor. The subjects were treated as a random effect. Repeated measures analysis of variance was also used for models with two within-factors (side: left/right; level: baseline/subanesthetic/anesthetic) to study the differences in *S*-ketamine–induced effects between the right and left hemispheres. Because there were no significant side-by-level interactions, except for $rCMRO_2$ in the cerebellum, all PET results are presented as mean values. Statistical analyses were conducted with SAS (version 8.2; SAS Institute Inc., Cary, NC). A two-sided $P$ value of less than 0.05 was considered statistically significant. To overcome multiplicity, the Tukey-Kramer correction was applied to $P$ values. Data are presented as mean ± SD if not otherwise stated.

**Voxel-based SPM Analysis.** As an additional method, SPM software[28] running under MATLAB (MATLAB 6.5; The MathWorks Inc., Natick, MA) was used to analyze the absolute changes in rCBF, $rCMRO_2$, and rGMR. SPM enables localization of statistically significant regional changes without having to define specific ROIs. Thus, changes outside the specified regions of the ROI analysis could be detected.

The subject's tissue tracer activity images were first computed into quantitative parametric CBF, $CMRO_2$, and GMR images as described in our previous articles.[14,26] The estimated values for the whole brain CBV were used in the calculations of the parametric images for $CMRO_2$. The SPM preprocessing was performed as described in our previous articles.[13,26,25] The images were smoothed using an isotropic gaussian filter of 12 mm full-width at half-maximum.

Subtraction analysis with T-contrasts was used to test *S*-ketamine–induced absolute changes between the conditions. The changes were considered significant at $P < 0.05$ (corrected for multiple comparisons). The visualizations (maximum intensity projections) were performed with T-contrast (height threshold) values of 3 and 8. The nonsignificant findings were discarded from the visualizations by adjusting the minimum cluster size (extend threshold, k).[29]

The Montreal Neurological Institute (McGill University, Montreal, Quebec, Canada) coordinates received from the statistical analysis were converted to Talairach coordinates[30] with "mni2tal" conversion software (Medical Research Council, Cognition and Brain Sciences

**Table 1. Summary of Hemodynamic, Respiratory, and Plasma Glucose Values during the Study**

| | No Drug | Subanesthetic *S*-ketamine | Anesthetic *S*-ketamine | Overall ANOVA, *P* Value |
|---|---|---|---|---|
| Mean arterial blood pressure, mmHg | 93.3 ± 6.5 | 108.3 ± 5.5‡ | 117.9 ± 8.5‡§ | 0.0002 |
| Heart rate, beats/min | 56.7 ± 7.8 | 69.7 ± 10.8‡ | 80.5 ± 12.8† | 0.0010 |
| Hematocrit, % | 41.3 ± 2.8 | 41.8 ± 2.2 | 42.4 ± 1.8 | NS |
| Peripheral oxygen saturation, % | 99.0 ± 0.4 | 99.3 ± 0.3 | 98.4 ± 0.5 | NS |
| Arterial oxygen saturation, % | 97.5 ± 0.5 | 97.5 ± 0.5 | 98.0 ± 0.5 | NS |
| End-tidal $CO_2$ during CBF scans, % | 5.4 ± 0.3 | 5.2 ± 0.3 | 5.4 ± 0.3 | NS |
| Arterial $CO_2$ partial pressure, mmHg | 41.0 ± 3.0 | 41.0 ± 3.4 | 43.0 ± 3.2 | NS |
| Plasma glucose concentration, mm | 5.4 ± 0.4 | No data available | 6.5 ± 0.8 | 0.0139 |

Values are given as group mean ± SD.

Statistically significant differences between *S*-ketamine *vs.* baseline (* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$) and anesthetic *vs.* subanesthetic *S*-ketamine (§ $P < 0.05$) are shown.

ANOVA = analysis of variance; CBF = cerebral blood flow; $CO_2$ = carbon dioxide; NS = not significant.

Unit, Cambridge, England).|||| For the localization, The Montreal Neurological Institute Space utility## and Talairach Daemon Software*** (University of Texas Health Science Center at San Antonio, San Antonio, TX)[31] were used.

## Results

The subjects remained fully cooperative during subanesthetic *S*-ketamine. Induction with zero-order infusion resulted in loss of consciousness (defined by failure to squeeze the investigators hand twice) in approximately 3.4 ± 1.1 min. However, two of the subjects remained clinically awake and followed given breathing instruction with occasional eye opening, although they did not respond to requests for hand squeezing. Because of these two subjects, clinical unresponsiveness was reached in 8.2 ± 4.1 min. Excessive salivation and some spontaneous motor activity was observed during anesthesia. Three of the subjects could be released home the same evening. Five of the subjects, however, had to spend the night at the research unit because of slight nausea and dizziness and were released the next morning.

All subjects experienced many of the typical ketamine-induced hallucinations during the subanesthetic *S*-ketamine, including sensations of traveling or floating (seven of eight), altered body-image (three of eight), and difficulties in the perception of reality and the surroundings (two of 8, for both). Two subjects reported that these sensations had been unpleasant. Squeezing the investigator's hand was most often reported (six of eight) as the last recollection before the loss of consciousness. The two most often reported first recollections after the anesthesia were the feeling of being surrounded by people (four of eight) and nausea (three of eight). None of the subjects reported any awareness during anesthesia. All subjects experienced postanesthetic emesis. Five subjects considered it the most unpleasant experience according to the interview on the next day and 10 months after the anesthesia. Three of the subjects reported that they would refuse to be anesthetized again with *S*-ketamine. None of the subjects experienced any "flashback" sensations during the 10-month follow-up period.

The measured mean serum *S*-ketamine concentration at the end of the subanesthetic infusion was 159 ± 21 ng/ml (sample I). During the induction of *S*-ketamine anesthesia, the subjects lost their consciousness at 1084 ± 144 ng/ml (sample II). The mean dose of *S*-ketamine needed for loss of consciousness was 1.1 ± 0.4 mg/kg. The measured mean serum *S*-ketamine concentrations after the $rCMRO_2$ (sample III) and rGMR (sample IV) scans during anesthesia were 1,931 ± 410 and 1,986 ± 518 ng/ml, respectively (fig. 1). The total *S*-ketamine dose was 10.4 ± 1.0 mg/kg during the study.

### *The Monitoring Parameters*

Heart rate was increased from baseline by 22.8% ($P < 0.001$) during subanesthetic *S*-ketamine and by 43.5% ($P = 0.001$) during anesthetic *S*-ketamine. The mean blood pressure was increased by 16.3% during subanesthetic *S*-ketamine and by 27.0% during anesthetic *S*-ketamine ($P < 0.001$ for both). The partial pressure of arterial blood carbon dioxide was not changed during the study, and there were no significant changes in $ET_{CO_2}$ values during the CBF assessments. No changes were detected in peripheral or arterial blood oxygen saturation or hematocrit during the study. *S*-ketamine anesthesia significantly increased plasma glucose concentration by 20.1% ($P = 0.014$; table 1).

### *ROI-based Analysis of PET Data*

**Subanesthetic *S*-ketamine.** Whole brain CBF was increased by 13.7% ($P = 0.035$; table 2 and fig. 2).

|||| Brett M: 1999. Available at: http://www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml. Accessed July 2, 2005.

## Pakhomov S, Steffener JR. 2001. Available at: http://www.ihb.spb.ru/~pet_lab/MSU/MSUMain.html. Accessed July 2, 2005.

*** Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, Rainey L, Kochunov PV, Nickerson D, Mikiten SA, Fox PT. 2000. Available at: http://ric.uthscsa.edu/research/body.html. Accessed July 2, 2005.

**Table 2. Absolute Regional Cerebral Blood Flow (ml · 100 $g^{-1}$ · $min^{-1}$) Values of Region-of-interest–defined Structures**

| Region | No Drug | Subanesthetic S-ketamine | Anesthetic S-ketamine | Overall ANOVA, P Value |
|---|---|---|---|---|
| Anterior cingulate | 56.68 ± 10.96 | 73.17 ± 10.54* | 94.69 ± 17.78† | 0.0008 |
| Posterior cingulate | 57.96 ± 7.41 | 61.85 ± 7.80 | 71.10 ± 15.73 | NS |
| Frontal cortex | 54.07 ± 5.97 | 65.28 ± 7.04* | 79.38 ± 15.54† | 0.0022 |
| Parietal cortex | 51.28 ± 6.32 | 56.09 ± 6.44 | 65.82 ± 7.72* | 0.0151 |
| Temporal cortex | 50.84 ± 4.54 | 54.16 ± 4.42 | 70.91 ± 12.52*§ | 0.0225 |
| Occipital cortex | 41.36 ± 3.69 | 44.13 ± 5.88 | 44.99 ± 5.53 | NS |
| Insula | 59.59 ± 8.84 | 75.19 ± 8.23‡ | 109.42 ± 15.81‡‖ | 0.0002 |
| Caudate | 52.18 ± 6.45 | 59.28 ± 8.49 | 67.38 ± 10.77* | 0.0276 |
| Putamen | 63.11 ± 8.74 | 72.18 ± 9.25* | 95.64 ± 19.19†‖ | 0.0075 |
| Thalamus | 63.57 ± 8.88 | 73.74 ± 5.89† | 105.43 ± 26.57* | 0.0039 |
| Cerebellum | 55.03 ± 6.26 | 62.57 ± 6.24† | 71.24 ± 17.33 | 0.0125 |
| Whole brain | 42.35 ± 5.26 | 47.86 ± 5.21* | 57.42 ± 8.62† | 0.0032 |

Values are given as group mean ± SD.

Statistically significant differences between S-ketamine *vs.* baseline (* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$) and anesthetic *vs.* subanesthetic S-ketamine (§ $P < 0.05$, ‖ $P < 0.01$) are shown.

ANOVA = analysis of variance; NS = not significant.

Regionally, CBF increased in the anterior cingulate, insula, frontal cortex, thalamus, putamen, and cerebellum by 14.1–31.6% ($P < 0.05$; table 2 and fig. 3A). No changes were detected in $CMRO_2$ (table 3 and fig. 3B).

**Anesthetic *S*-ketamine.** Whole brain CBF was increased by 36.4% ($P = 0.006$) from baseline (table 2 and fig. 2). With the exception of the posterior cingulate, occipital cortex, and cerebellum, CBF was increased (by 29.8–86.5%; $P < 0.05$) in all studied regions. In addition, CBF was increased from the subanesthetic values in the insula, putamen, temporal cortex by 31.5–47.0% ($P < 0.05$; table 2 and fig. 3A). Although $CMRO_2$ was increased from baseline only in the frontal cortex by 15.7% ($P = 0.007$), it was in addition increased from the subanesthetic values in the insula by 24.2% and in the thalamus by 16.6% ($P < 0.05$ for both; table 3 and fig. 3B). GMR was increased from baseline only in the thalamus by 11.7% ($P = 0.010$; table 4 and fig. 3C).

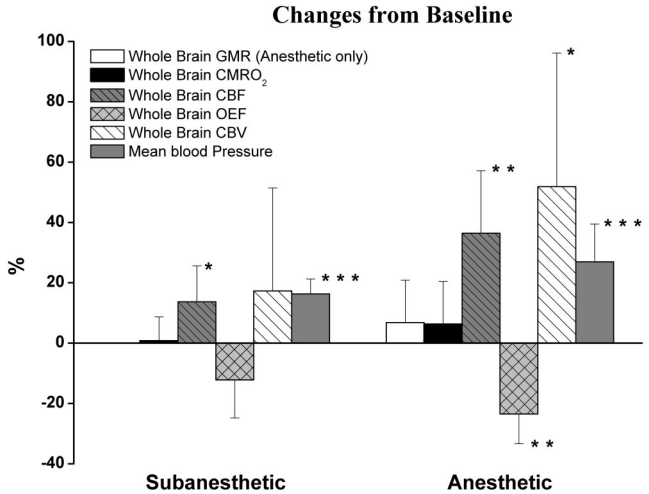


**Fig. 2. The changes from baseline (%) in the whole brain values of glucose metabolic rate (GMR; anesthetic only), cerebral metabolic rate of oxygen ($CMRO_2$), cerebral blood flow (CBF), oxygen extraction fraction (OEF), estimate for cerebral blood volume (CBV), and mean blood pressure induced by target-controlled *S*-ketamine infusion aiming at subanesthetic (150 ng/ml) and anesthetic (1,500–2,000 ng/ml) concentrations are shown. Significant changes: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.**

*Calculated Variables (CBV, OGI, and OEF)*

**Subanesthetic *S*-ketamine.** The estimated mean whole brain CBV was 3.3% (not significantly different from the baseline value 2.9%). OEF was decreased in the insula, thalamus, and putamen by 17.1–24.6% ($P < 0.05$; table 5 and fig. 3D).

**Anesthetic *S*-ketamine.** The estimated whole brain CBV was 4.2% during *S*-ketamine anesthesia. It was significantly increased from baseline by 51.9% ($P = 0.011$; fig. 2). The whole brain OEF was decreased from baseline by 23.5% ($P = 0.005$). With the exception of the posterior cingulate, occipital cortex, and caudate, OEF was decreased (by 19.2–37.0%; $P < 0.01$) in all studied regions (table 5 and fig. 3D). The mean whole brain OGI was not significantly changed during *S*-ketamine anesthesia from the baseline value of 4.6.

*Voxel-based SPM Analysis of PET Data*

**Subanesthetic *S*-ketamine.** The clusters representing CBF increases reached parts of the frontal cortex and insula bilaterally, the temporal cortex and limbic lobe on the right, and the claustrum on the left hemisphere (fig. 4, *1*). No changes in $CMRO_2$ were detected. More detailed localizations of the clusters in figure 4 are presented on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org.

**Anesthetic *S*-ketamine.** Cerebral blood flow was increased in a global manner. The clusters of the most significant (at a T threshold value of 8) CBF increases were located bilaterally around the central and lateral sulci reaching parts of the frontal, temporal, and parietal cortices and the insula and claustrum (fig. 4, *2*). $CMRO_2$

**Table 3. Absolute Regional Cerebral Metabolic Rate of Oxygen (ml · 100 $g^{-1}$ · $min^{-1}$) Values of Region-of-interest–defined Structures**

| Region | No Drug | Subanesthetic *S*-ketamine | Anesthetic *S*-ketamine | Overall ANOVA, *P* Value |
|---|---|---|---|---|
| Anterior cingulate | 4.00 ± 0.69 | 4.33 ± 0.93 | 4.90 ± 0.99 | 0.0449 |
| Posterior cingulate | 4.69 ± 0.98 | 4.76 ± 0.72 | 5.09 ± 0.83 | NS |
| Frontal cortex | 3.51 ± 0.28 | 3.88 ± 0.39 | 4.06 ± 0.40* | 0.0120 |
| Parietal cortex | 3.74 ± 0.47 | 3.75 ± 0.48 | 3.97 ± 0.53 | NS |
| Temporal cortex | 3.73 ± 0.23 | 3.80 ± 0.29 | 4.26 ± 0.55 | NS |
| Occipital cortex | 3.43 ± 0.35 | 3.45 ± 0.27 | 3.63 ± 0.38 | NS |
| Insula | 4.44 ± 0.41 | 4.24 ± 0.42 | 5.25 ± 0.93† | 0.0418 |
| Caudate | 3.51 ± 0.39 | 3.71 ± 0.73 | 4.01 ± 0.65 | NS |
| Putamen | 4.48 ± 0.52 | 4.28 ± 0.46 | 4.66 ± 0.74 | NS |
| Thalamus | 4.51 ± 0.50 | 4.17 ± 0.32 | 4.86 ± 0.55† | 0.0102 |
| Cerebellum | 4.02 ± 0.79 | 4.14 ± 0.74 | 3.93 ± 0.73 | NS |
| Whole brain | 2.98 ± 0.47 | 2.98 ± 0.37 | 3.13 ± 0.36 | NS |

Values are given as group mean ± SD.

Statistically significant differences between *S*-ketamine *vs.* baseline (* $P < 0.01$) and anesthetic *vs.* subanesthetic *S*-ketamine († $P < 0.05$) are shown.

ANOVA = analysis of variance; NS = not significant.

increases were mainly (75% of the voxels) located in white matter or outside the neural tissue. However, some of the $CMRO_2$ increases in gray matter were located in the same regions with the most significant changes in CBF (fig. 4, *3*). $CMRO_2$ was decreased only in a small part of the right frontal lobe (fig. 4, *4*). GMR increases were located bilaterally around the central and lateral sulci reaching parts of the frontal, parietal, and temporal cortices and the insula (fig. 4, *5*). GMR was decreased in a small region including parts of the cerebellum and the temporal and occipital cortices (fig. 4, *6*). More detailed localizations of the clusters in figure 4 are presented on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org.

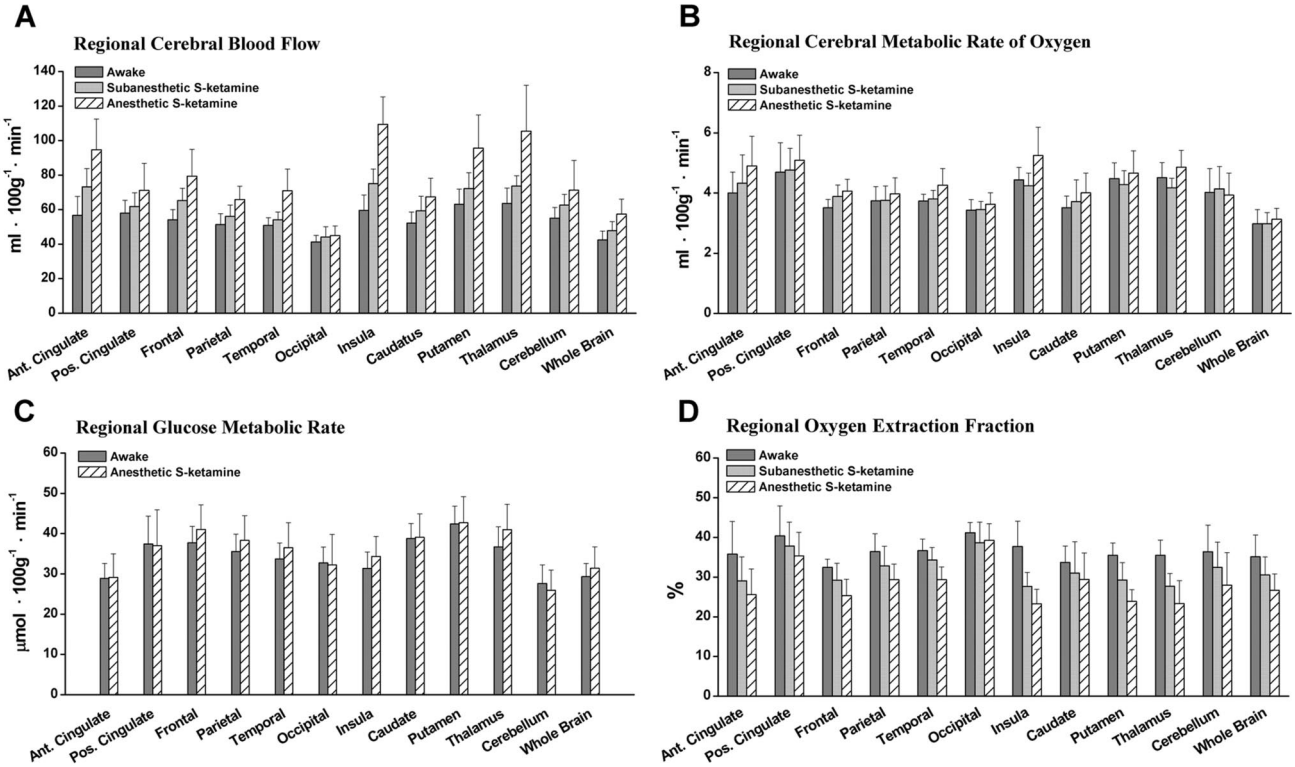


**Fig. 3. Absolute left–right group mean ± SD values of regional cerebral blood flow (*A*; ml · 100 $g^{-1}$ · $min^{-1}$), metabolic rate of oxygen (*B*; ml · 100 $g^{-1}$ · $min^{-1}$), glucose metabolic rate (*C*; µmol · 100 $g^{-1}$ · $min^{-1}$), and oxygen extraction fraction (*D*); in 12 region-of-interest-defined structures are shown at baseline and during target-controlled *S*-ketamine infusion aiming at subanesthetic (cerebral blood flow, metabolic rate of oxygen, and oxygen extraction fraction only) and anesthetic concentrations. Statistics are presented in tables 2–5. Ant. = anterior; Pos. = posterior.**

**Table 4. Absolute Regional Cerebral Glucose Metabolic Rate ($\mu$mol · 100 g$^{-1}$ · min$^{-1}$) Values of Region-of-interest–defined Structures**

| Region | No Drug | Anesthetic S-ketamine | Overall ANOVA, P Value |
|---|---|---|---|
| Anterior cingulate | 28.88 ± 3.68 | 29.10 ± 5.86 | NS |
| Posterior cingulate | 37.41 ± 6.95 | 37.03 ± 8.85 | NS |
| Frontal cortex | 37.77 ± 4.01 | 41.04 ± 6.08 | NS |
| Parietal cortex | 35.50 ± 4.37 | 38.30 ± 6.15 | NS |
| Temporal cortex | 33.74 ± 3.97 | 36.50 ± 6.21 | NS |
| Occipital cortex | 32.74 ± 3.94 | 32.22 ± 7.60 | NS |
| Insula | 31.38 ± 4.04 | 34.36 ± 4.93 | NS |
| Caudate | 38.76 ± 3.76 | 39.07 ± 5.78 | NS |
| Putamen | 42.40 ± 4.43 | 42.68 ± 6.49 | NS |
| Thalamus | 36.73 ± 4.96 | 41.01 ± 6.27 | 0.0100 |
| Cerebellum | 27.63 ± 4.59 | 25.92 ± 5.04 | NS |
| Whole brain | 29.35 ± 3.25 | 31.38 ± 5.34 | NS |

Values are given as group mean ± SD.

Statistically significant differences between S-ketamine anesthesia *vs.* baseline are shown.

ANOVA = analysis of variance; NS = not significant.

## Discussion

To be suitable for neurosurgical patients, an anesthetic agent should reduce neuronal activity and result in parallel and uniform decreases in cerebral metabolism and blood flow. An ideal anesthetic would also offer fast recovery, unspoiled reactivity to carbon dioxide and blood pressure, intact CBF–metabolism coupling, and effective neuroprotection without increasing intracranial pressure (or CBV).[5,32] In addition to its neuroprotective properties,[17,33] *S*-ketamine is an anesthetic with a rapid onset and short duration of action. Furthermore, it does not seem to affect cerebral autoregulation when administered during propofol anesthesia.[5]

In the current study, the whole brain CBF was significantly increased during *S*-ketamine anesthesia, whereas there were no corresponding changes in $CMRO_2$ or GMR. This resulted in a decrease in the whole brain OEF but no change in OGI. Also subanesthetic *S*-ketamine increased the whole brain CBF but did not effect $CMRO_2$. Although the estimated whole brain CBV was not changed during subanesthetic *S*-ketamine, it was significantly increased during anesthesia. The mean blood pressure was increased in a concentration-dependent manner.

The effects of subanesthetic *S*-ketamine on human CBF, $CMRO_2$, and CBV seem to be quite similar to those of racemic ketamine observed in our previous PET study.[13] There seems to be only one previous study on the CBF and metabolic effects of sole anesthetic ketamine in humans.[16] By using the Kety-Schmidt method for the whole brain CBF and appropriate arteriovenous content difference values for metabolic substances, the racemate (intravenous bolus of 2 mg/kg followed by another 1-mg/kg bolus after 5 min) was shown to increase CBF, with no significant changes in $CMRO_2$ or GMR. In addition, decreased cerebral vascular resistance was observed. Although Takeshita *et al.* [16] could not present any regional data at the time, their findings on

**Table 5. Absolute Regional Cerebral Oxygen Extraction Fraction (%) Values of Region-of-interest–defined Structures**

| Region | No Drug | Subanesthetic S-ketamine | Anesthetic S-ketamine | Overall ANOVA, P Value |
|---|---|---|---|---|
| Anterior cingulate | 35.80 ± 8.19 | 29.06 ± 6.01 | 25.58 ± 6.43† | 0.0064 |
| Posterior cingulate | 40.39 ± 7.59 | 37.81 ± 6.03 | 35.33 ± 5.95 | NS |
| Frontal cortex | 32.44 ± 2.11 | 29.20 ± 4.27 | 25.32 ± 4.13† | 0.0021 |
| Parietal cortex | 36.44 ± 4.47 | 32.85 ± 4.93 | 29.34 ± 3.94† | 0.0024 |
| Temporal cortex | 36.64 ± 2.95 | 34.31 ± 3.13 | 29.35 ± 3.19†§ | 0.0033 |
| Occipital cortex | 41.20 ± 2.57 | 38.61 ± 5.22 | 39.28 ± 4.17 | NS |
| Insula | 37.71 ± 6.34 | 27.64 ± 3.54* | 23.28 ± 3.62†# | 0.0016 |
| Caudate | 33.67 ± 4.18 | 31.03 ± 7.89 | 29.39 ± 6.71 | NS |
| Putamen | 35.50 ± 3.07 | 29.23 ± 4.40* | 23.88 ± 2.93‡§ | 0.0008 |
| Thalamus | 35.51 ± 3.84 | 27.70 ± 3.23† | 23.36 ± 5.74† | 0.0002 |
| Cerebellum | 36.40 ± 6.70 | 32.44 ± 6.35 | 27.99 ± 8.17† | 0.0011 |
| Whole brain | 35.11 ± 5.47 | 30.55 ± 4.51 | 26.69 ± 4.09† | 0.0085 |

Values are given as group mean ± SD.

Statistically significant differences between S-ketamine *vs.* baseline (* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$) and anesthetic *vs.* subanesthetic S-ketamine (§ $P < 0.05$) are shown.

ANOVA = analysis of variance; NS = not significant.

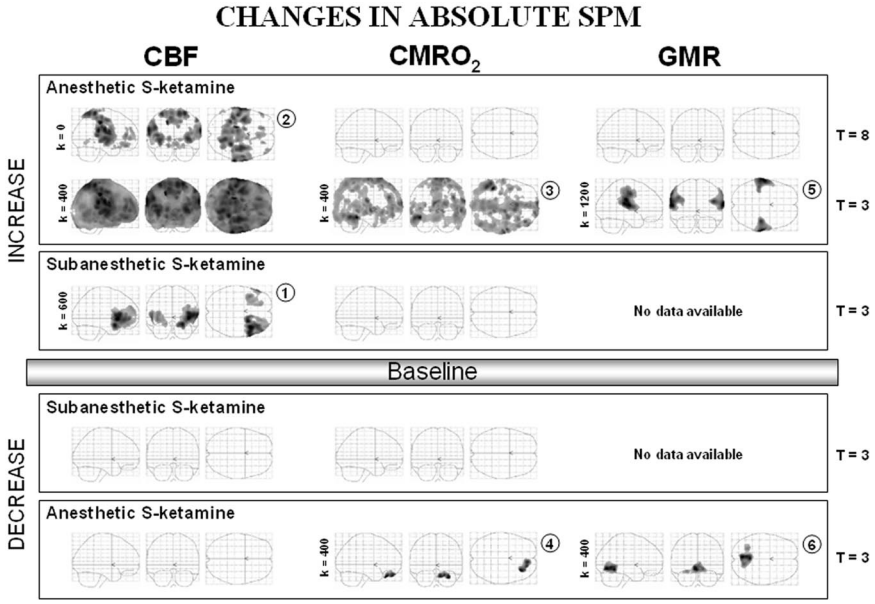


**Fig. 4. The results of the voxel-based (Statistical Parametric Mapping [SPM]) analysis. Regions of statistically significant ($P < 0.05$, corrected for multiple comparisons) absolute changes from baseline in cerebral blood flow (CBF), metabolic rate of oxygen ($CMRO_2$), and glucose metabolic rate (GMR) induced by target-controlled *S*-ketamine infusion aiming at subanesthetic (150 ng/ml) and anesthetic (1,500–2,000 ng/ml) concentrations are shown at statistical criteria levels (height threshold, T) of 3 and 8. The nonsignificant clusters (with $P$ values > 0.05) were discarded from the visualizations by adjusting the minimum cluster size (extend threshold, k). The circled numbers (*1–6*) correspond to the tables of stereotaxic localizations presented on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org. For details, see Materials and Methods, Data Analysis, Voxel-based SPM Analysis.**

the global effects of racemic ketamine are now supported by our results on the effects of *S*-ketamine anesthesia assessed with more sophisticated methodology.

The oxygen-to-glucose index is defined as a relation of oxygen and glucose consumption. In normal conditions, approximately six oxygen molecules are consumed for each glucose molecule, yielding a stoichiometric OGI value close to 6.[34,35] If glucose is consumed more than oxygen, OGI is decreased, suggesting anaerobic glycolysis. Because OGI was not changed from baseline during *S*-ketamine anesthesia, it is unlikely that anaerobic glycolysis occurred.

Positron emission tomography and functional MRI are both widely used for detecting neuronal activation. In PET, activation is represented as regionally *increased CBF*. Functional MRI, however, detects changes in *oxygen availability* as blood oxygen level–dependent signal is increased in the activated region.[36] Nevertheless, neither of these measurements reveals the whole phenomenon underneath. In the activated brain region, the increases in CBF and GMR transiently exceed the increase in $CMRO_2$, resulting in an increase in oxygen availability (supply exceeds the demand).[36,37] The whole phenomenon can, however, be detected with PET if all of these three variables are assessed during one study session.[35] In PET, increased oxygen availability is reflected as a decrease in OEF.

In the current study, OEF was decreased in nearly all regions during *S*-ketamine anesthesia. However, the majority of these decreases probably do not represent *S*-ketamine–induced neuronal activation because GMR was increased only in the thalamus.[36,37] Similarly, the majority of observed increases in CBF most likely do not indicate neuronal activation. Therefore, GMR assessment is of vital importance when studying the effects of *S*-ketamine on neuronal activation.

In addition to *S*-ketamine–induced effects on the whole brain, some regional changes were also observed. The only significant anesthesia-induced GMR increase in the ROI analysis was located in the thalamus. Neuronal activation in this brain region would, in fact, seem logical because anesthetic doses of racemic ketamine have been associated with increased electrophysiologic activity in the human thalamus.[38] Although *S*-ketamine anesthesia increased $CMRO_2$ from baseline only in the frontal cortex, $CMRO_2$ was in addition increased from the subanesthetic values in the thalamus and insula. Furthermore, even though the ROI analysis revealed no GMR changes in the frontal cortex or insula during *S*-ketamine anesthesia, the clusters representing the anesthesia-induced GMR increases in the voxel-analysis partly reached these brain regions as well. Thus, the metabolic components were increased in the corresponding brain regions.

Although CBF was increased in excess to both metabolic components (*i.e.*, $CMRO_2$ and GMR), it is interesting that some of the most significant anesthesia-induced increases in all these three variables were located around the central and lateral sulci in the voxel analysis. Similar localization of these changes could imply that in this particular small cortical region, CBF was, in fact, increased to serve the needs for increased metabolism. In general, this fronto-parieto-temporal region, including the primary motor and sensory cortices and the superior temporal gyrus, is involved in proprioception and motor performance.[39] The activation of the superior temporal gyrus has particularly been associated with the recognition of seen body movements and speech-associated facial expressions.[40–42]

The voxel-based analysis revealed increased CBF, $CMRO_2$, and GMR in the insula during *S*-ketamine anesthesia. Electrical stimulation of this brain region has been

associated with changes in blood pressure and heart rate,[43,44] heart rhythm,[45] respiration, gastric motility, salivation, and norepinephrine secretion.[46] In addition, the insula has been suggested to participate in pain processing.[47,48] It is therefore possible that many of the ketamine-induced secondary effects (analgesia, hemodynamic effects, salivation, emesis, and others) are linked to this brain area. Although ketamine-induced stimulation on the cardiovascular system has been proposed to be unrelated to baroreceptor desensitization,[49,50] it is of interest that the brain regions most often associated with baroreceptor control are the insula and thalamus.[51,52]

It has recently been demonstrated that both isoflurane- and halothane-induced unconsciousness are associated with decreased GMR in the thalamus and disrupted thalamocortical connection to the primary and supplementary motor association cortices.[53] Therefore, it is somewhat surprising that *S*-ketamine was found to increase GMR in both the thalamus and the cortical regions associated with motor function. The possible changes in thalamocortical connectivity during ketamine-induced unconsciousness remain to be studied.

Subanesthetic *S*-ketamine induced more localized, smaller increases in CBF, with no changes in $CMRO_2$ or CBV. Because of the long half-life (110 min) of the $^{18}$F-isotope, we could not perform a GMR measurement during subanesthetic *S*-ketamine. However, the effects of subanesthetic *S*-ketamine on human cerebral GMR have been studied previously using a zero-order *S*-ketamine infusion and PET.[18] In that study, widespread GMR increases (19.6–27.4%) were associated with a 379-ng/ml plasma concentration of *S*-ketamine. When these GMR results are compared with the CBF increases induced by subanesthetic *S*-ketamine in the current study, the changes are of similar magnitude. Still, caution is needed when these results are compared because the infusion schemes were different and *S*-ketamine concentration was 138% higher in the study by Vollenweider *et al.* [18] Because *S*-ketamine has a propensity to increase CBF in a concentration-dependent manner, it would be tempting to speculate that CBF increases would probably exceed the increases in GMR if the same drug concentrations were used.

The *S*-enantiomer of ketamine has been estimated to possess approximately twice the anesthetic potency of the racemate in humans.[54,55] Thus, Vollenweider *et al.* [18] were able to perform their GMR study under a surprisingly high and yet subanesthetic concentration of *S*-ketamine. The target concentration level (150 ng/ml) for the subanesthetic *S*-ketamine in the current study was chosen based on our previous studies where the target concentration level of 300 ng/ml racemic ketamine induced significant changes in CBF and GMR while still maintaining full cooperation of the subjects.[13,14]

Estimation of anesthetic depth is difficult with ketamine. Vital signs are mostly useless because increased blood pressure or heart rate may well be suggestive of either insufficient anesthetic depth or too high a concentration of ketamine. Therefore, awareness during anesthesia was one of the primary concerns in the current study. The minimum anesthetic serum concentration of *S*-ketamine in healthy adults has been demonstrated to be approximately 1,200 ng/ml.[54] Slow recovery of the subjects was somewhat surprising and suggests that a slightly excessive target concentration level was used. Importantly, none of the subjects reported any awareness during anesthesia.

In the kinetic modeling for $CMRO_2$, CBV is normally assumed to be constant (approximately 3%). This is a fair assumption under normal awake conditions and during subanesthetic doses of racemic ketamine, which have been demonstrated to induce only negligible effects on regional CBV.[13] Decreased cerebral vascular resistance has, however, been observed in humans *anesthetized* with racemic ketamine.[16] Therefore, anesthetic doses of ketamine may have an effect on cerebral vascular tone. Brain imaging with PET and $^{15}$O-labeled carbon monoxide is a well-established method for measuring cerebral blood volume. However, it was not possible to include this assessment into the current study without exposing the subjects to unacceptably large doses of radiation. As an alternative, the whole brain estimate for CBV was obtained as a kinetic modeling parameter from each dynamic $[^{15}O]O_2$ activity acquisition image using the whole brain ROIs. Although not as accurate as a separate $^{15}$O-carbon monoxide PET measurement, this estimation enabled more precise kinetic modeling for $rCMRO_2$ as blood volume was no longer assumed to be constant.

To meet the demanding requirements for neuroanesthesiologic use, *S*-ketamine should have induced parallel and uniform decreases in CBF, $CMRO_2$, and GMR. However, anesthetic *S*-ketamine greatly increased CBF and blood volume with only minor changes in metabolism. Regardless of its suggested neuroprotective properties, pure *S*-ketamine anesthesia hardly offers the optimal conditions for a neurosurgical patient.

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