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Cerebral Blood Flow, Blood Volume, and Mean Transit Time Responses to Propofol and Indomethacin in Peritumor and Contralateral Brain Regions

Perioperative Perfusion-weighted Magnetic Resonance Imaging in Patients with Brain Tumors

Mads Rasmussen, M.D., Ph.D.,* Niels Juul, M.D.,* Søren M. Christensen, M.M.Sc., Ph.D.,† Kristjana Y. Jónsdóttir, M.Sc., Ph.D.,‡ Carsten Gyldensted, M.D., Ph.D.,§ Peter Vestergaard-Poulsen, M.Sc., Ph.D.,‖ Georg E. Cold, M.D., Ph.D.,# Leif Østergaard, M.Sc., M.D., Ph.D.**

ABSTRACT

Background: The regional cerebral blood flow (CBF) response to propofol and indomethacin may be abnormal in patients with brain tumors. First, the authors tested the hypothesis that during propofol anesthesia alone and combined with indomethacin, changes in CBF, cerebral blood volume (CBV), and plasma mean transit time (MTT) differ in the peritumoral tissue compared with the contralateral normal brain region. Second, the authors tested the hypothesis that CBF and CBV are reduced and MTT is prolonged, in both regions during propofol anesthesia and indomethacin administration compared with propofol alone.

Methods: The authors studied eight patients subjected to craniotomy under propofol–fentanyl anesthesia for supratentorial brain tumors. Magnetic resonance imaging, including perfusion- and diffusion-weighted and structural sequences, was performed (1) on the day before surgery, (2) before and (3) after administration of indomethacin in the propofol–fentanyl anesthetized patient, and (4) 2 days after surgery. Maps of CBF, CBV, and MTT were calculated. The regions of interest were peritumoral gray matter and opposite contralateral gray matter. Analysis of variance was used to analyze flow data.

Results: Propofol anesthesia was associated with a median 32% (range, 3–61%) and 47% (range, 17–67%) reduction in CBF in the peritumoral and contralateral regions, respectively.

The interaction between intervention with propofol and indomethacin and region of interest was not significant for any flow modalities. Neither intervention nor region was significant for MTT, CBF, and CBV ($P > 0.05$).

Conclusion: The CBF, CBV, and MTT responses to propofol and indomethacin are not different in the peritumoral region compared with contralateral brain tissue. Indomethacin did not further influence regional CBF, CBV, and MTT during propofol anesthesia.

What We Already Know about This Topic

- Both propofol and indomethacin reduce cerebral blood flow in normal brain
- The combined effect of these drugs on cerebral blood flow surrounding brain tumors is unknown

What This Article Tells Us That Is New

- Propofol reduced cerebral blood flow in peritumor brain tissue in eight patients similar to its reduction in normal brain tissue contralaterally, and this was not altered by indomethacin
- Propofol and indomethacin are unlikely to cause a unilateral blood flow imbalance in patients with brain tumors

PROPOFOL has been suggested as the drug of choice during craniotomy.[1] Compared with volatile anesthetics, propofol significantly reduces intracranial pressure (ICP) and improves cerebral perfusion pressure in patients undergoing craniotomy for brain tumors.[1] The reduction in ICP may be secondary to a decrease in cerebral blood volume (CBV) caused by cerebral vasoconstriction.[2–6] Only one study has provided detailed information of cerebral hemodynamics in tumor and peritumoral brain regions during propofol anesthesia. In a rabbit brain tumor model, Cenic *et al.*[7] found that CBV and cerebral blood flow (CBF) were lower in tumor, peritumor, and contralateral normal tissue

* Staff Anesthesiologist, # Assistant Professor Emeritus, Department of Neuroanesthesia, † Biomedical Engineer, § Professor, ‖ Associate Professor, Department of Neuroradiology, ‡ Statistician, ** Professor, Department of Neuroradiology, Center of Functionally Integrative Neuroscience, Århus University Hospital.

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Address correspondence to Dr. Rasmussen, Department of Neuroanesthesia, Århus University Hospital, Nørrebrogade 44, 8000 Århus C, Denmark. mads.rasmussen@vest.rm.dk.

during propofol anesthesia compared with isoflurane. Whether this observation applies to humans has not been investigated.

Indomethacin has been suggested as a therapeutic option to treat intracranial hypertension in patients with head injury[8–9] and in patients undergoing craniotomy for brain tumors.[10] In contrast to standard treatment strategies, such as hyperventilation and osmotic therapy, intravenous administration of indomethacin rapidly reduces CBF and ICP along with increases in the mean arterial blood pressure and cerebral perfusion pressure.[10–12] Because of the vasoconstrictive action on the cerebral vessels, the use of indomethacin may theoretically be associated with a risk of inducing cerebral ischemia in patients with brain pathology. By using diffusion-weighted magnetic resonance imaging (MRI), we demonstrated in a previously published part of this study that administration of indomethacin was not associated with ischemic damage in propofol-anesthetized patients with brain tumors.[13] The extent to which indomethacin improves or reduces cerebral perfusion in the peritumor and contralateral brain regions has, however, not been investigated previously. In patients with brain tumor, the flow response to propofol and indomethacin in the peritumoral region and the contralateral hemisphere may differ owing to tumor size and morphology, abolished autoregulation, and altered carbon dioxide reactivity.[14,15]

Perfusion-weighted MRI allows rapid measurements of CBF, CBV, and plasma mean transit time (MTT) with high spatial resolution.[16–20] The aim of this study was to examine hemodynamic changes across tissue types during propofol anesthesia and indomethacin. In particular, we aimed to test the hypothesis that during propofol anesthesia alone and combined with indomethacin, changes in CBF, CBV, and MTT differ in the peritumoral tissue compared with the contralateral normal brain region. Second, we tested the hypothesis that CBF and CBV are reduced and MTT is prolonged, in both regions during propofol anesthesia and indomethacin administration compared with propofol alone.

Materials and Methods

The Research Ethics Committee of the County of Aarhus, Denmark, approved the study. The investigation was conducted in accordance with Note for Guidance on Good Clinical Practice. Monitoring of the study was performed by the Good Clinical Practice Unit, Århus University Hospital, Århus, Denmark.

Patient Population

After written informed consent was obtained, nine patients (American Society of Anesthesiologists physical status I or II) undergoing supine-positioned elective craniotomy for supratentorial brain tumors of 3 cm or larger (measured as the largest diameter in any plane on magnetic resonance [MR] images) were included in the study. Exclusion criteria were age younger than 18 yr or older than 70 yr, pregnancy or nursing, history of allergic reactions to prostaglandin inhibitors, arterial hypertension (diastolic pressure $>$ 110 mmHg), cardiac failure (New York Heart Association class III or IV), moderate to severe chronic pulmonary insufficiency, renal or hepatic dysfunction/disease, peptic ulcer, and treatment with indomethacin or other nonsteroid anti-inflammatory drugs.

Experimental Protocol

The detailed experimental protocol has been reported previously and a simplified time sequence diagram is shown in figure 1.[13] Briefly, imaging was performed with a 1.5-T GE Signa Imager (GE Medical Systems, Milwaukee, WI). The first MRI examination was performed in the awake patient the day before surgery. MRI sequences consisted of a three-dimensional T1-weighted spoiled gradient recall sequence, a T2-weighted sequence, and a fluid-attenuated inversion recovery sequence, which were used to obtain images for outlining the extent of tumor, edema, and older ($>$ 12 h) ischemic lesions. To detect acute ischemic lesions, an axial diffusion-weighted sequence was acquired, and on the basis of this, maps of the apparent diffusion coefficient were calculated.

Perfusion imaging was performed by dynamic spin-echo echo planar imaging during a bolus injection of 0.2 mmol/kg of Gadolinium-DTPA (Magnevist®; Schering AG, Berlin, Germany), injected at a rate of 5 ml/s, with an 8-s delay, using an MR-compatible power injector (Medrad, Pittsburgh, PA). This bolus was immediately followed by injection of an equal volume of physiologic saline, also at the rate of 5 ml/s. Eleven or twelve slices were obtained, covering the tumor area. Fifty images were obtained in each of the slices during the bolus passage, and accordingly 550 or 600 images were obtained during the 55-s acquisition time. The acquisition parameters were time of repetition/time of echo = 1,500/75 ms, flip angle 20°, 96 × 96 resolution, 24-cm field of view, 5-mm slice thickness and 1.5-mm interslice gap with a 55-s acquisition time.

A postcontrast T1-weighted spoiled gradient recall sequence was acquired for determination of tumor contrast enhancement and to assess tumor grade. The duration of the examination was 30–35 min.

On the day of surgery, the patient was anesthetized and transported to the MR scanner. The second MRI examination was performed before administration of indomethacin to evaluate the possible ischemic and cerebral hemodynamic effects of the initial propofol–fentanyl anesthesia. MRI was performed approximately 70 min after induction of anesthesia. Indomethacin was then administered as an intravenous bolus dose of 0.2 mg/kg followed by infusion 0.2 $mg \cdot kg^{-1} \cdot h^{-1}$. The third MRI examination was initiated 5 min after administration of the indomethacin bolus dose, with the perfusion-weighted sequence performed 21–22 min after administration of the indomethacin bolus dose. Both MRI examinations consisted of the same sequences as the initial scan (first MRI examination), except for the fluid-attenuated inversion recovery sequence, which would be insensitive to acute ischemic lesions. The indomethacin infusion was terminated after completion of the third MRI

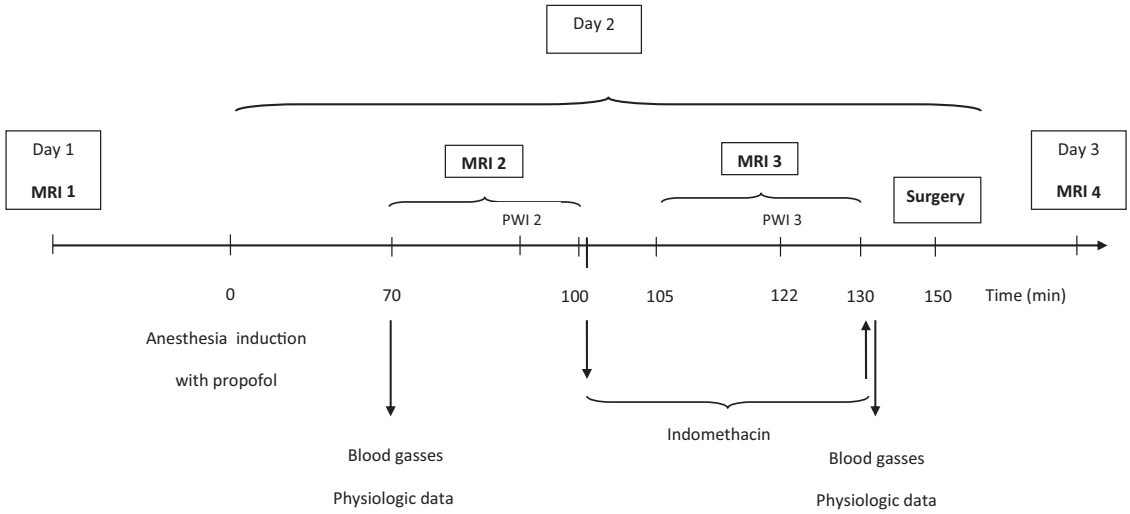

Fig. 1. Time sequence diagram. First magnetic resonance imaging (MRI) examination (MRI 1) was performed in the awake patient the day before surgery. On the day of surgery, the patient was anesthetized and transported to the MR scanner. Second MRI examination (MRI 2) was performed in the propofol-anesthetized patient approximately 70 min after anesthesia induction. Indomethacin was administered as a bolus dose followed by an infusion, and the MRI examination was repeated (third MRI examination [MRI 3]) with the perfusion-weighted imaging (PWI) sequence performed approximately 22 min after indomethacin administration. After completion of MRI 3, the anesthetized patient was transported to the operating theater for surgery. Two days after surgery, a fourth MRI examination (MRI 4) was performed in the awake patient. Blood gases and physiologic data were collected immediately before commencement of the second MRI examination and again immediately after termination of MRI 3.

examination. Data concerning mean arterial blood pressure, $S_{jv}O_2$, arterio–venous oxygen difference ($AVDO_2$), arterial oxygen tension (Pa_{O_2}), and arterial carbon dioxide tension (Pa_{CO_2}) were collected immediately before commencement of the second MRI examination and again immediately after termination of the third MRI examination. The duration of the two examinations, including indomethacin administration, was approximately 60 min. After completion of the MRI examinations, the anesthetized patient was transported to the operating theater for surgery.

The fourth MRI examination was performed in the awake patient 2 days after surgery to detect possible "late" ischemic lesions and to measure postsurgery cerebral hemodynamics, using the same MRI protocol as the first MRI examination.

Tumor Size, Tumor Localization, and Histopathological Diagnosis

Tumor size (calculated from the modified spheric volume equation: $\frac{4}{3} \times \pi \times r_1 \times r_2 \times r_3$), tumor localization, and the degree of midline shift were determined by an experienced certified neuroradiologist (C.G.) from the structural MR images obtained from the first MRI examination. The histopathological diagnosis was obtained from the neuropathology report.

Anesthesia and Monitoring

The patients were premedicated with diazepam (5–15 mg) orally 1 h before anesthesia. For induction, propofol (1.2–2.5 mg/kg), supplemented with fentanyl (2–4 $\mu g \cdot kg^{-1} \cdot h^{-1}$), was used. Cisatracurium (0.2 mg/kg) was administered to facilitate tracheal intubation. Anesthesia was maintained with propofol (6–12 $mg \cdot kg^{-1} \cdot h^{-1}$) and fentanyl (1.5–3 $\mu g \cdot kg^{-1} \cdot h^{-1}$). Neuromuscular blockade was maintained with cisatracurium and monitored by train-of-four stimulation. Controlled ventilation (fraction of inspired oxygen [FIo_2] 50–60% by oxygen-air) was applied, and the patients were ventilated with Pa_{CO_2} and Pa_{O_2} levels, which we attempted to keep between 30–40 mmHg and greater than 100 mmHg, respectively. A decrease in systolic pressure exceeding 20 mmHg, compared with the preoperative level, was treated with 5–10 mg of intravenous ephedrine. Normal saline of 15 ml/kg was infused for the first hour after induction followed by normal saline (2–4 $ml \cdot kg^{-1} \cdot h^{-1}$). Moreover, to counteract the blood pressure decrease observed after induction of anesthesia, 500 ml of 6% hydroxyethyl–starch was infused over a period of 30 min. Monitoring consisted of continuous electrocardiography, pulse oximetry (Datex® AS3; Datex, Helsinki, Finland), and rectal temperature monitoring. After induction of anesthesia, a radial artery catheter was inserted for continuous mean arterial blood pressure monitoring and blood sampling. A jugular bulb catheter was inserted retrogradely into the internal jugular vein for jugular bulb pressure monitoring and jugular venous blood sampling. The tip of the catheter was placed high in the jugular bulb, and the position was confirmed by X-ray control. After stable physiologic conditions were ensured, the patient was transferred to the MR scanner. During the MRI examinations, hemodynamic parameters were continuously monitored with an MR-compatible monitor, and controlled ventilation was applied with an MR-compatible ventilator.

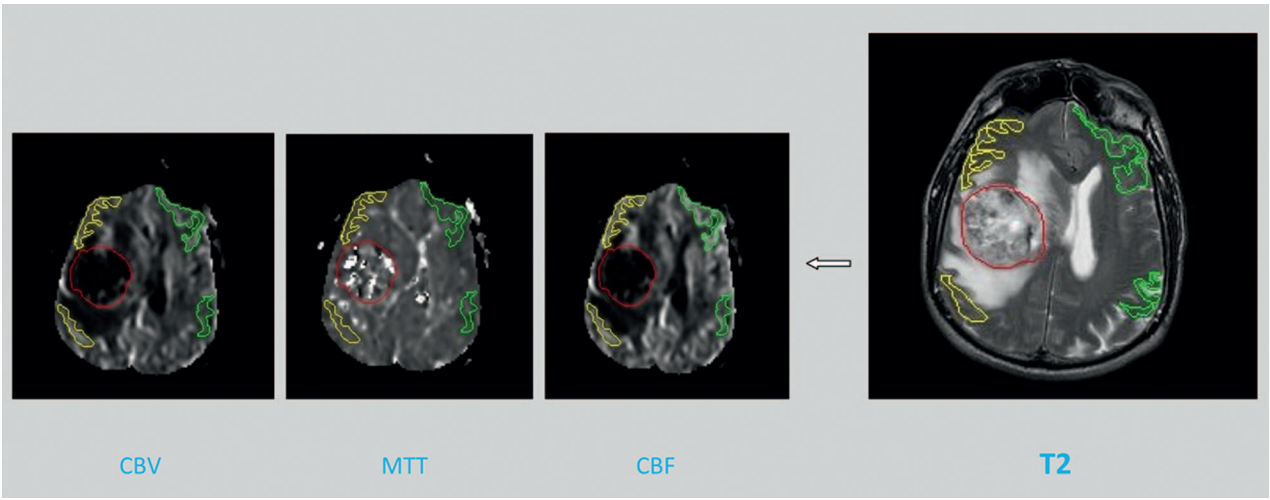

Fig. 2. Perfusion maps and regions of interest. Maps of cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) were calculated. The regions of interest considered were peritumoral gray matter (*yellow*) and opposite contralateral gray matter (*green*). Regions of interest were identified and manually drawn on structural T2 images and transferred to the CBF, CBV, and MTT maps using commercially available software. T2 = T2-weighted magnetic resonance image.

Determination of Perfusion-weighted Maps

Maps of CBF, CBV, and MTT were calculated using a noninvasively determined arterial input function and singular value decomposition deconvolution as described previously.[16–19]

In each patient, a single perfusion-weighted imaging slice was examined. This slice was selected to display a representative part of the tumor with corresponding and identifiable peritumoral gray matter. The regions of interest considered were peritumoral gray matter and opposite contralateral gray matter. Regions of interest were identified and manually drawn by a trained and certified neuroradiologist (C.G.) on the structural T1 and T2 images and transferred to the CBF, CBV, and MTT maps using commercially available software (Cheshire, Hayden Image Processing Solutions, Boulder, CO) (fig. 2).The contralateral region of interest was drawn to mimic the size and location of the peritumor region of interest (fig. 2).

Statistical Analysis

We performed ANOVA of log-transformed data measured during propofol induction and indomethacin administration for all three modalities with intervention and region as within-subject factors and subject as a random factor. Changes in CBF, CBV, and MTT at both timepoints in the peritumoral region relative to the contralateral region were calculated. Signed Wilcoxon tests were used to compare physiologic parameters measured during propofol with changes observed after indomethacin administration. Physiologic parameters are presented by median values and ranges. Statistical significance was considered at the 5% level. We used SPSS software, version 15.0, (SPSS Inc., Chicago, IL).

Results

Because of technical difficulties with generating the perfusion maps, one patient (Patient 6) was excluded from the study. Thus, eight patients were included. In Patient 5, it was not possible for the neuropathologist to determine the tumor type. In Patient 3, it was not possible to insert a jugular bulb catheter. Thus, no $S_{jv}O_2$ and $AVDO_2$ measurements were performed.

Detailed patient characteristics, histopathological diagnoses, and tumor image characteristics have been previously published.[13] Briefly, age ranged from 29 to 68 yr. The tumor type was neuroepithelial tumor in one case, oligodendroglioma in four cases, glioblastoma in one case, gliosarcoma in one case, and unspecified tumor in one case. The tumor size ranged from 6.5–69.1 cm^3.

Induction doses of fentanyl and propofol were 2.5 $\mu g/kg$ (1.8–3.2 $\mu g/kg$) and 1.2 mg/kg (0.7–1.80 mg/kg), respectively, and maintenance doses were 1.8 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (1.4–2.20 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and 7.0 $mg \cdot kg^{-1} \cdot h^{-1}$ (4.5–10 $mg \cdot kg^{-1} \cdot h^{-1}$) respectively. The time interval from induction of anesthesia to the perfusion-weighted sequence was 86 min (71–91 min).

A detailed presentation of physiologic parameters measured during propofol anesthesia and after administration of indomethacin has been previously published,[13] which are summarized as follows: mean arterial blood pressure (propofol = 99 mmHg [90–103 mmHg]; indomethacin = 98 mmHg [74–122 mmHg]; $P = 0.41$), $S_{jv}O_2$ (propofol = 51% [40–61%]; indomethacin = 43% [37–63%]; $P = 0.12$), $AVDO_2$ (propofol = 4.4 $mmol \cdot l^{-1}$ [2.7–4.6 $mmol \cdot l^{-1}$]; indomethacin = 4.7 $mmol \cdot l^{-1}$ [2.9–4.9 $mmol \cdot l^{-1}$]; $P = 0.075$), Pa_{CO_2} (propofol = 34 mmHg [30–41 mmHg]; indomethacin = 33 mmHg [29–40 mmHg]; $P = 0.31$), and PaO_2 (propofol = 211 mmHg [85–326 mmHg]; indomethacin = 263 mmHg [108–348 mmHg]; $P = 0.03$).

Changes in Flow Parameters

Compared with the condition in awake patients, propofol anesthesia was associated with a median 32% (range, 3–61%) and 47% (range, 17–67%) reduction in CBF in the

Table 1. Median Relative Difference Between the Two Interventions and the Two Regions, Respectively

	MTT	CBF	CBV
Propofol *vs*. indometacin	1.11 (0.95–1.30)	0.99 (0.84–1.16)	1.09 (0.91–1.31)
Peritumoral *vs*. contralateral	0.96 (0.84–1.09)	1.02 (0.87–1.19)	0.99 (0.93–1.06)

Median relative difference including 95% confidence intervals between the two interventions and the two regions, respectively, for mean transit time (MTT), cerebral blood flow (CBF), and cerebral blood volume (CBV). The median relative difference is calculated on the basis of ANOVA of log-transformed data measured during propofol and indomethacin for all three modalities with intervention and region as within-subject factors and subject as a random factor.

peritumoral and contralateral regions, respectively. CBF was not further reduced by indomethacin in any region.

The ANOVA demonstrated that the interaction between intervention with propofol and indomethacin and the peritumoral and contralateral regions was not significant for any flow modalities. Neither intervention nor region were significant for MTT, CBF, and CBV ($P > 0.05$). The 95% confidence intervals for the median relative difference between the two interventions and regions are shown in table 1. Changes in CBF, CBV, and MTT in the peritumoral region relative to the contralateral region for each patient are demonstrated in figures 3 to 5.

Discussion

Although propofol anesthesia was associated with a reduction in CBF (median 32% in peritumoral and 47% in the contralateral region), we were not able to prove the hypothesized differences across tissue type or any further hemodynamic effects with the additional intervention with indomethacin. In agreement with our earlier findings,[13] we found no evidence of flow reductions that would precipitate ischemic damage.

Early studies in awake subjects have indicated that regional CBF in brain tumor patients is abnormal in the tumor area and in the brain tissue immediately surrounding it.[15,21] There are few data in the literature on the effects of propofol and vasoactive drugs on regional changes in the cerebral circulation in patients with brain tumors. The findings in this study are in agreement with a human study by Schmieder *et al.,*[22] who demonstrated that the reduction in CBF velocity after propofol anesthesia was not statistically significant on the tumor side compared with the contralateral region. However, in two patients, they reported a different perfusion pattern with an increase in peritumoral CBF velocity after propofol induction.[22] Similar flow patterns were also found in our study. In two patients, we observed an increase in CBF (ranging from 2 to 17%) in both peritumoral and contralateral gray matter after induction with propofol. In contrast, Schregel *et al.*[14] reported that propofol reactivity was lower on the tumor side compared with the nontumor side in patients with large brain tumors. Regional differences in CBF was also found in an experimental study by Cenic *et al.,*[7] who demonstrated that CBF and CBV were highest in the tumor region and lowest in the contralateral normal tissue in a rabbit tumor model. Methodological differences regarding technique of measuring CBF, tumor location, tumor size, tumor histophathology, and species can explain the different findings between the studies.

Propofol caused a substantial reduction in CBF in both the peritumoral and contralateral regions, which is in agreement with the literature.[23,24] Comparing CBF during anesthesia relative to the awake state is, however, associated with some limitations. Several variables could possibly have changed, for example, ventilation (spontaneous *vs.* controlled) and hydration state could have changed because of preoperative fasting. Unfortunately, $Paco_2$ data were not measured at day 1, and the possibility exists that the flow changes observed in these patients were partly caused by variations in $Paco_2$. None of the patients, how-

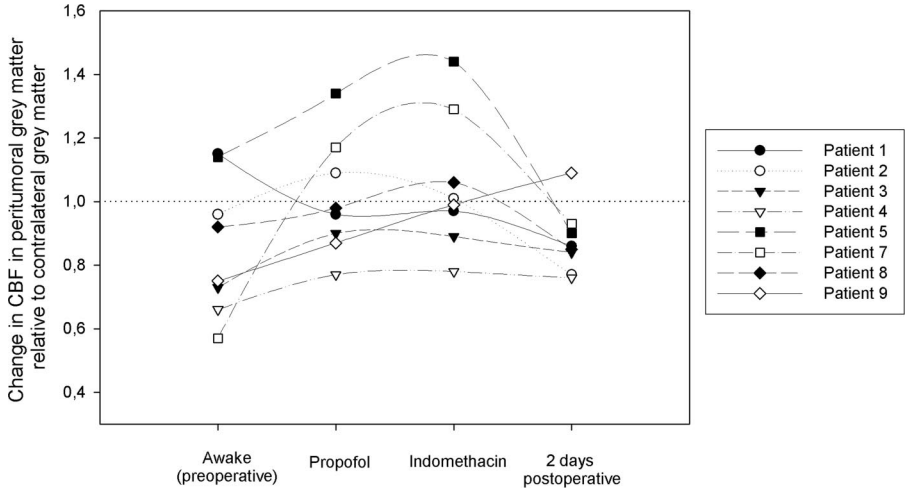

Fig. 3. Change in cerebral blood flow (CBF) in peritumoral gray matter relative to contralateral gray matter at four different timepoints.

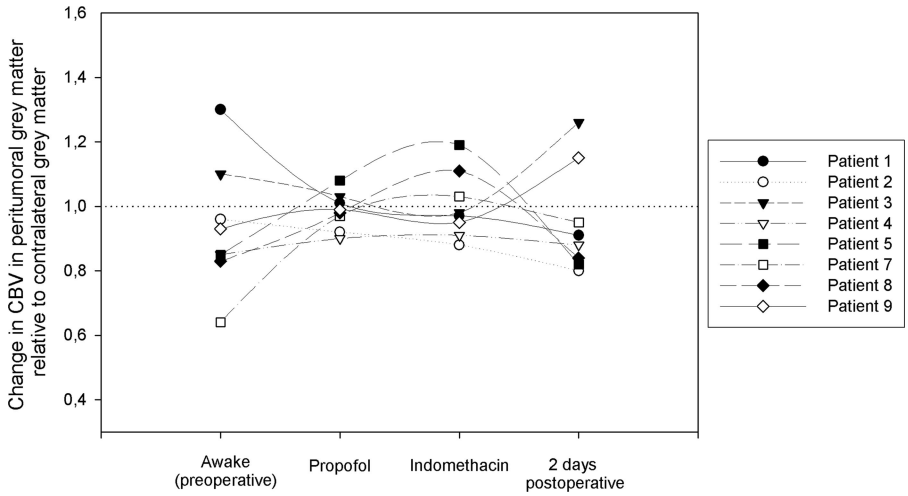

Fig. 4. Change in cerebral blood volume (CBV) in peritumoral gray matter relative to contralateral gray matter at four different timepoints.

ever, had pulmonary disease, and they were all awake and conscious during the first MRI examination. Therefore, we find it appropriate to assume normocapnia in these subjects. Mean arterial blood pressure did not change significantly after propofol induction, and we assume that altered fluid status caused by preoperative fasting did not influence the changes in CBF.

The finding that indomethacin, administered during propofol anesthesia, had little or no additional effect on CBF in most patients is in accordance with the nonsignificant changes in $S_{jv}O_2$ and $AVDO_2$. In addition, a previous study demonstrated that indomethacin did not influence ICP in propofol-anesthetized patients undergoing craniotomy for cerebral tumors.[25] In that study, CBF velocity was reduced by 50% after propofol without any further reduction in CBF after an indomethacin infusion.[25] This observation is in contrast to a recent experimental study by Rasmussen *et al.*,[12] where propofol caused a 35% reduction in CBF followed by an additional 14% reduction in CBF after injection of indomethacin. We speculate that the observed difference in the propofol-induced reduction of CBF and degree of vasoconstriction between the previous clinical study,[25] the current study, and the experimental study by Rasmussen *et al.*[12] may explain the additional 14% reduction of CBF and ICP in response to indomethacin. Indomethacin may, therefore, have a limited effect in terms of further reducing ICP during propofol anesthesia in experimental and clinical use. Given the fact that that both experimental and clinical studies have demonstrated a significant effect of indomethacin on ICP in volatile-anesthetized subjects,[10,12] it is suggested that the main indication for the use of indomethacin is ICP reduction in gas-anesthetized individuals.

This study has several limitations. First, because of the inherent logistical complexity of MRI of anesthetized patients, the study was limited in size. Second, there is a variability in the study regarding tumor size, tumor location, and histopathology. In this regard, the study population is not homogenous. Some of the patients had large tumors, and the impact on the surrounding brain may have caused regional areas of hypoperfusion. In these areas, the flow measurements may be prone to errors because of difficulty with obtaining sufficient MRI signals in the hypoperfused areas of the brain.[26] In addition, there are differences in vessel proliferation and hence tumor and peritu-

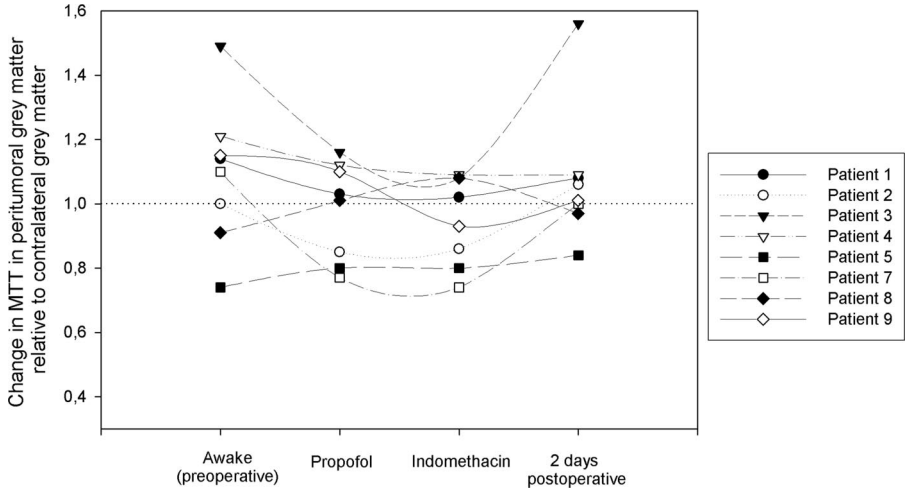

Fig. 5. Change in mean transit time (MTT) in peritumoral gray matter relative to contralateral gray matter at four different timepoints.

moral perfusion, depending on the tumor type, which may have influenced the CBF and CBV measurements. Third, we report normalized CBF and CBV values relative to contralateral values rather than reporting absolute values. This follows a previously reported normalization approach[16,17] while reducing inaccuracies in absolute CBF and CBV values caused by partial volume effects of arterial voxel signals. The MTT estimates are, however, quantitative and allow comparisons across patients and anesthetic regimes.

We conclude that CBF and CBV response to propofol and indomethacin was comparable in the peritumoral and contralateral normal brain tissue. This finding indicates that propofol may decrease ICP in patients with brain tumors without causing blood flow imbalance between both sides of the brain, thus limiting the risk of worsening right to left (or left to right) mass effect.

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