Human cerebral microcirculation and oxygen saturation during propofol-induced reduction of bispectral index†

K. U. Klein1*, K. Fukui1, P. Schramm1, A. Stadie2, G. Fischer2, C. Werner1, J. Oertel2 and K. Engelhard1

1 Department of Anaesthesiology and 2 Department of Neurosurgery, University Medical Centre of the Johannes Gutenberg-University, Langenbeckstrasse 1, 55131 Mainz, Germany

*Corresponding author. E-mail: kuklein@uni-mainz.de

Editor’s key points

- This study investigates the effects of propofol-induced changes in bispectral index (BIS) on cerebral microcirculation and oxygenation during craniotomies.
- In 2 mm cerebral depth, an increase in propofol dosage resulted in increased oxygen saturation (srvO2) without reduction of capillary venous blood flow (rvCBF).
- Difference in oxygen content (avDO2) and approximated cerebral metabolic rate of oxygen (acCMRO2) decreased with an increase in propofol dosage in 2 mm cerebral depth.
- Alterations in BIS showed no effect on rvCBF, srvO2, and haemoglobin amount (rvHb) or on avDO2 or acCMRO2 in 8 mm cerebral depth.
- These findings suggest that the CBF/CMRO2 ratio is altered by propofol in a regionally specific fashion.

Background. Propofol reduces cerebral blood flow (CBF) secondary to cerebral metabolic depression. However, in vitro and in vivo studies demonstrate that propofol directly dilates the vascular smooth muscle. This study investigates the effects of propofol-induced changes in bispectral index (BIS) on cerebral microcirculation and oxygenation during craniotomies.

Methods. In 21 craniotomy patients undergoing routine craniotomy, anaesthesia was maintained with propofol 4–10 mg kg−1 h−1 and remifentanil 0.1–0.4 μg kg−1 min−1. Propofol concentration was adjusted to achieve higher BIS (target 40) or lower BIS (target 20). Regional measurements of capillary venous blood flow (rvCBF), oxygen saturation (srvO2), and haemoglobin amount (rvHb) at 2 mm (grey matter) and 8 mm (white matter) cerebral depth were randomly performed at higher and lower BIS by combined laser-Doppler flowmetry and spectroscopy. Calculations: approximated arteriovenous difference in oxygen content (avDO2) and cerebral metabolic rate of oxygen (acCMRO2).

Results. Human cerebral microcirculation and oxygen saturation were assessed at propofol dosages 5.1 (2.3) mg kg−1 h−1 [BIS 40 (9)] and 7.8 (2.1) mg kg−1 h−1 [BIS 21 (7)]. Propofol-induced reduction in BIS resulted in increased srvO2 (P=0.018), and decreased avDO2 (P=0.025) and acCMRO2 (P=0.022), in 2 mm cerebral depth, while rvCBF and rvHb remained unchanged. In 8 mm cerebral depth, srvO2, rvCBF, rvHb, and also calculated parameters avDO2 and acCMRO2 remained unaltered.

Conclusions. Findings suggest alteration of the CBF/CMRO2 ratio by propofol in cortical brain regions; therefore, it might be possible that propofol affects coupling of flow and metabolism in the cerebral microcirculation.

Keywords: bispectral index; cerebral blood flow; cerebral oxygen saturation; laser-Doppler flowmetry; neuromonitoring; oximetry; propofol

Accepted for publication: 29 May 2011

Propofol (2,6-diisopropylphenol) is a short-acting, i.v. hypnotic agent widely used for the induction and maintenance of general anaesthesia. In vivo studies confirmed that propofol reduces cerebral blood flow (CBF) secondary to a decrease in cerebral metabolic rate of oxygen (CMRO2) under maintenance of the coupled relationship between CMRO2 and CBF.1 2 However, there is some evidence that propofol also modulates the CBF/CMRO2 ratio.3 Studies in rats, hamsters, and pigs demonstrate that propofol induces generalized vasodilation through the arterial tree.4–6 This effect is present in large cerebral arteries (e.g. pig basilar artery) exposed to clinically relevant propofol concentrations. However, in cerebral microvessels (e.g. rabbit pial arteries), vasodilation occurs only with high (e.g. 10–4 mol litre−1) concentrations of propofol.6–8 This suggests dose-related regionally specific vascular effects of propofol along with changes in cerebral metabolism.

A novel device (O₂C-device, oxygen-to-see-device, LEA Medizintechnik GmbH, Giessen, Germany) allows for instantaneous regional measurement of cerebral microcirculation and oxygen saturation.9 10 Capillary venous CBF (rvCBF), oxygen saturation (srvO2), and haemoglobin amount (rvHb) are determined in cerebral microcirculation using combined laser-Doppler flowmetry (rvCBF) and photo-spectrometry (srvO2, rvHb). Additional measurement of arterial blood gas analysis allows for calculation of arteriovenous difference in oxygen content (avDO2) and simultaneous measurements of rvCBF and srvO2 allow...
calculation of approximated cerebral metabolic rate of oxygen (aCMRO$_2$).

The objective of the present study was to investigate the effect of two different concentrations of propofol (i.e. different depths of anaesthesia) on human cerebral microcirculation (rvCBF, rvHb), cerebral oxygenation saturation (srvO$_2$), and calculated metabolic parameters (avDO$_2$, aCMRO$_2$). It was hypothesized that in the presence of functional neurovascular coupling, suppression of brain metabolism by propofol would lead to (i) decreases in rvCBF; (ii) increases in srvO$_2$; and (iii) no change in avDO$_2$.

Methods

This study was approved by the Research Ethical Care Committee of the state of Rhineland-Palatinate, Germany [Ref: 837.136.05 (4794)] and registered with EudraCT (Ref: 2005-001646-17). After written patient informed consent, 21 ASA II–III patients undergoing elective intracranial surgery were included in the study. Anaesthesia was induced i.v. with sufentanil 0.3 mg kg$^{-1}$, propofol 2 mg kg$^{-1}$, and atracurium 0.5 mg kg$^{-1}$. The trachea was intubated and lungs were ventilated (pressure control) using an inspiratory oxygen fraction of 0.5 and a PEEP of 5 mbar. Anaesthesia was continued by infusion of propofol 5–6 mg kg$^{-1}$ h$^{-1}$ and remifentanil 0.1–0.4 µg kg$^{-1}$ min$^{-1}$. Patient monitoring included a five-lead ECG, heart rate (HR), peripheral haemoglobin (Hb) oxygen saturation (Sp$_{O_2}$), bladder temperature (Temp), and bispectral index (BIS) measurement of the non-operated hemisphere. All patients received a radial arterial line for continuous measurement of mean arterial pressure (MAP) and intermittent blood gas analyses. At the time of craniotomy, the O$_2$C-device for the assessment of cerebral microcirculation and oxygen saturation was attached to macroscopically healthy cortical brain tissue.

Intraoperative measurements

The measurement principle of the device relies on the transmission of near infrared and visible light to tissue and has been described in detail in previous studies.$^9,10$ The complete set-up of the device including connection of the measurement probe, start of the personal computer, and calibration of the probe to white light required a 5 min period. The light source of the measurement probe was sterilized with alcohol solution. The probe was covered with sterile polyurethane protective for ultrasound transducers (Ultrasound 87110, Microtek Medical, Zutphen, The Netherlands) and flushed with warm saline solution. Patients were randomly assigned to the first measurement at lower (target BIS = 20) or higher (target BIS = 40) BIS. After introduction of anaesthesia, propofol dosage was adapted (4–10 mg kg$^{-1}$ h$^{-1}$) until target BIS target level was reached. After a stabilization period for 30 min, when BIS remained stable, the probe was applied carefully without pressure to macroscopically healthy surface of cortical tissue next to the site of surgery. The probe was then covered with swabs to exclude artificial light effects. After a stabilization period of 20 s, the first set of measurements was performed resulting in 40–60 single measurements. Thereafter, the probe was removed. Levels of initially lower BIS were altered to higher BIS or vice versa by adjustment (increase or decrease) of propofol dosage. At steady-state conditions, the probe was replaced to the identical area of cortical tissue and measurements were repeated in the same manner.

All data obtained were stored electronically. Physiological variables including MAP, HR, Sp$_{O_2}$, Temp, F$_{I_{O_2}}$, Hb, haematocrit (Hc), and arterial blood gases were controlled and maintained constant over time. When appropriate, MAP was stabilized by repetitive administration of the sympathomimetic agent Akrinor® (bolus of 0.25 ml i.v.). A 2 ml ampoule of Akrinor® (AWD Pharma, Dresden, Germany) contains cafedrine-hcl 200 mg and theodrenaline-hcl 10 mg. The substance acts predominantly on β$_1$- and β$_2$-receptors and elevates arterial pressure by an increase in venous return and cardiac output. The effect of Akrinor® on cerebral vasculature has not been investigated. A WarmTouch® (Covidien, Boulder, CO, USA) system was applied to maintain core temperature, which was measured via the urine catheter. In the case of intraoperative bleeding, Hb concentration was maintained > 8.0 mg dl$^{-1}$ by repetitive administration of 2 units (250–300 ml) of red blood cells.

Statistical analysis

Oxygen content of arterial blood (CaO$_2$) was calculated using the equation: 

$$\text{CaO}_2 = [1.39 \times \text{Hb} (\text{g dl}^{-1}) \times (S_aO_2 (\%)/100)] + [P_{O_2} (\text{mm Hg}) \times 0.0034].$$

Venous partial pressure ($P_{vO_2}$) of cerebral tissue was converted from srvO$_2$ values based on the Hb oxygenation curve.$^{11}$ Venous oxygen content (CvO$_2$) was determined via the equation: 

$$\text{CvO}_2 = [1.39 \times \text{Hb} (\text{g dl}^{-1}) \times (\text{srvO}_2 (\%)/100)] + [P_{vO_2} (\text{mm Hg}) \times 0.0034].$$

The arteriovenous difference in oxygen content (avDO$_2$) was calculated using the formula: 

$$\text{avDO}_2 = \text{CoO}_2 (\text{ml dl}^{-1}) - \text{CvO}_2 (\text{ml dl}^{-1}).$$

Approximated cerebral metabolic rate of oxygen (aCMRO$_2$) was calculated using the formula: 

$$\text{aCMRO}_2 = \text{rvCBF (arbitrary units)}/5 \times \text{avDO}_2 (\text{ml dl}^{-1}).$$

A factor of 5 was used to bring the measured (relative) rvCBF values to the same scale as the (absolute) CBF data obtained from the literature. This transformation was performed to produce aCMRO$_2$ values ranging in comparable limits to real CMRO$_2$ values. However, aCMRO$_2$ (arbitrary units) data represent approximated values and cannot be compared with absolute measurements of CMRO$_2$ (mg dl$^{-1}$). The Mann–Whitney test was used and $P$-values of < 0.05 were considered significant. Analyses were performed using the statistical software R (http://www.r-project.org). Figures were plotted using GraphPad Prism (Version 5.0 b, GraphPad Software Inc., La Jolla, CA, USA). Data are presented as mean ± SD.

Results

Twenty-one patients were recruited and measurements were completed in 15 patients. In three patients, measurements...
could not be performed because of intraoperative bleeding which was not caused by the probe. In another three patients, the craniotomy was too small (<3 cm) for adequate probe placement. There were no hardware, probe, or user failures of the O2C-device. The set-up time of the device was 5 (2) min. During the hospital stay and routine neurosurgical follow-up examinations, no adverse effects including bleeding, infection, tissue damage, and neurological deficit were observed that could be attributed to the cortical positioning of the probe.

Patients were comparable with respect to intracranial pathology, patient characteristics, and surgical covariates (Table 1). Normal propofol dosage was 5.1 (2.3) mg kg\(^{-1}\) h\(^{-1}\) [BIS 40 (9)] and the higher propofol dosage was 7.8 (2.1) mg kg\(^{-1}\) h\(^{-1}\) [BIS 21 (7); \(P<0.001;\) Fig. 1]. Physiological variables remained within a range of 10% change (Table 2).

At a higher propofol dosage of 7.8 (2.1) mg kg\(^{-1}\) h\(^{-1}\) [BIS 21 (7)], srvO\(_2\) (\(P=0.018\)) increased in 2 mm cerebral depth in comparison with a normal propofol dosage of 5.1 (2.3) mg kg\(^{-1}\) h\(^{-1}\) [BIS 40 (9)], while rvCBF and rvHb remained unchanged (Fig. 2). Likewise, calculated parameters avDO\(_2\) (\(P=0.025\)) and acCMRO\(_2\) (\(P=0.022\)) decreased in 2 mm cerebral depth with increased propofol dosage (Fig. 3). Altered propofol dosage had no impact on measured (rvCBF, srvO\(_2\), rvHb) or calculated (avDO\(_2\), acCMRO\(_2\)) parameters in 8 mm cerebral depth (Figs 2 and 3).

**Discussion**

We found that an increase in propofol dosage did result in increased srvO\(_2\) in 2 mm cerebral depth without reduction in rvCBF. Likewise, calculated parameters avDO\(_2\) and acCMRO\(_2\) decreased with an increase in propofol dosage. We also found that alterations in BIS showed no effect on measured (srvO\(_2\), rvCBF, rvHb) or calculated (avDO\(_2\), acCMRO\(_2\)) parameters in 8 mm cerebral depth. These findings suggest that the CBF/CMRO\(_2\) ratio is altered by propofol in a regionally specific fashion.

**Cortical capillary venous blood flow (rvCBF)**

Although much is known about the regulation of CBF and CMRO\(_2\), information with regard to the human cerebral microcirculation is limited.\(^{12}\) *In vitro*, propofol inhibits extracellular calcium influx through voltage-gated calcium channels inducing vasodilation, while *in vivo* CBF decreases dose-dependently with propofol.\(^{4-6}\) This effect is likely related to a dose-dependent depression of CMRO\(_2\). In the present study, changes of propofol concentration had no impact on rvCBF in 2 and 8 mm cerebral depth (Fig. 2). Former studies performed with the O2C-device revealed similar mean rvCBF values and confirmed the present results, in that changes of propofol concentration (4 vs 6 mg kg\(^{-1}\) h\(^{-1}\)) had no influence on rvCBF.\(^{9,10}\) The lack of rvCBF decrease despite reduction in BIS may relate to direct microvascular dilation. This infers that cortical coupling of metabolism and flow is disturbed by propofol. The neurovascular coupling relationship is intrinsically sensitive to different levels of anaesthesia and may be impaired (non-linear correlation) or abolished (no correlation) during deep anaesthesia.\(^{13}\) Another explanation is that some i.v. anaesthetics (e.g. propofol, thiopental) may alter the capillary perfusion leading to impairment of oxygen extraction capabilities.\(^{14,15}\) A recent human study demonstrates that propofol collapses capillaries and thereby decreases capillary blood flow in the sublingual mucosa.\(^{12}\) This phenomenon could not be confirmed by the present study. At this time, it appears to be wise, however, to consider avoiding propofol administration in patients with reduced microcirculatory function such as in severe organ dysfunction, sepsis, or

**Table 1** Patient characteristics, intracranial pathology, cardiovascular risk factors, and region of cortical measurements; data are presented as median (25–75th percentile or inter-quartile range) or incidence of observations

| Age (yr) | 47 (35–61) |
| Height (cm) | 169 (158–178) |
| Weight (kg) | 76 (68–83) |
| Body mass index (kg m\(^{-2}\)) | 26 (24–28) |
| ASA status (I–VI) | 2 (2–3) |
| Gender (M/F) | 9/6 |
| Glioblastoma (n/15) | 4/15 |
| Meningioma (n/15) | 1/15 |
| Temporal lobe epilepsy (n/15) | 2/15 |
| Cerebral metastasis (n/15) | 3/15 |
| AV-malformation, epidermoid, other (n/15) | 5/15 |
| Arterial hypertension (n/15) | 1/15 |
| Diabetes mellitus (n/15) | 1/15 |
| Smoker (n/15) | 1/13 |
| Frontal cortex measurement (n/15) | 3/15 |
| Temporal cortex measurement (n/15) | 9/15 |
| Parietal cortex measurement (n/15) | 3/15 |

**Fig 1** Frontal BIS of the non-operated hemisphere in dependency of i.v. propofol dosage (mg kg\(^{-1}\) h\(^{-1}\)).
shock. However, propofol has been shown to be neuroprotective in animal experiments. The neuroprotective effect of propofol is attributed to its antioxidant property, the potentiation of GABA-A mediated inhibition of synaptic transmission, and the inhibition of glutamate release. Cortical capillary venous oxygen saturation (srvO₂) As arterIALIZED blood transits through cerebral vasculature oxygen is extracted from cerebral tissue. Owing to the high CMRO₂, pericapillary PO₂ gradients are profound in cerebral grey matter. The present study showed mean srvO₂ values of 44% in 2 mm and 59% in 8 mm cerebral depth at BIS of 40 (9) vs higher propofol dosage [7.8 (2.1) mg kg⁻¹ h⁻¹, BIS 21 (7)]. An increase in propofol dosage [5.1 (2.3) mg kg⁻¹ h⁻¹, BIS 40 (9) vs 7.8 (2.1) mg kg⁻¹ h⁻¹, BIS 21 (7)] resulted in increased srvO₂ presumably caused by the metabolic depressant effect of propofol. avDO₂ decreased from 10.2 to 7.2 mg dl⁻¹ in 2 mm cerebral depth with an increase in propofol dosage (Fig. 3). Cerebral grey matter is the area with the highest synaptic activity and metabolic demand. It seems, therefore, reasonable that srvO₂ increases in 2 mm cerebral depth with an increase in propofol dosage. Animal studies determined an oxygen saturation of 54–59% at the venous end of cortical capillaries in rat cerebral cortex. Clinical studies revealed a mean venous cortical oxygen saturation between 40% and 70%. Studies in humans using the O₂C-device measured cortical srvO₂ between 40% and 70%. In accordance with the present study, different mean srvO₂ values in 2 mm (47%) and 8 mm (54%) cerebral depth have been described. A normal (5–7.5 mg dl⁻¹) avDO₂ would suggest that CBF is coupled to CMRO₂, while an elevated avDO₂ would indicate uncoupling or inadequate CBF (relative ischaemia). The authors highlight, however, that under anaesthesia with propofol, a relatively large amount (41–56%) of oxygen is extracted from cerebral tissue.

Cortical capillary venous Hb amount (rvHb)

The filling of cerebral microvessels is dependent on capillary density, recruitment, arterial upstream, and venous drainage of blood. Mean rvHb levels were within normal limits.
between 80 and 96 arbitrary units and indicate good blood filling of microvessels. Unchanged \( \text{rvHb} \) at altered propofol dosages assumes constant capillary filling and adequate venous return of blood. \( \text{rvHb} \) measurement could be of diagnostic value in the case of extreme alterations of vessel upstream or downstream such as arterial occlusion or pronounced venous stasis.

**Bispectral index**

A linear relationship between reduction in CMRO2 and decreasing BIS has been demonstrated during propofol anaesthesia. Furthermore, a positive correlation was found for BIS and propofol brain effect-site concentration. Therefore, the authors assume that a change in BIS from BIS 40 (9) (normal anaesthetic state) to 21 (7) (deep anaesthetic state) reflects a suppression in CMRO2 (Fig. 1). In 14 of the 15 patients, BIS decreased after an increase in propofol concentration; however, one patient showed a paradoxical increase in BIS (Fig. 1). To our knowledge, this phenomenon has not been described in the literature and may be caused by a measurement problem or artifact. BIS is mainly influenced by additive hypnotics, opioids, or inhalation agents. Neuromuscular blocking agents, choline esterase inhibitors, \( \beta \)-blockers, or electric signals may produce BIS artifacts. In the present study, propofol and remifentanil were the only drugs administered. Remifentanil demonstrated potent synergy with propofol in affecting BIS and may affect BIS readings at higher drug concentrations. However, remifentanil dosage was only minimally altered during experiments in the present study and effects on BIS are unlikely.

**Limitations**

BIS has been measured at the non-operated hemisphere and reflects CMRO2 contralateral to the site of measurement of cerebral microcirculation and oxygen saturation. However, the authors assume that BIS reflects a normal [BIS 40 (9)] and deep [BIS 21 (7)] anaesthetic state in both hemispheres. This study was possible because of the use of a novel device combining laser-Doppler flowmetry and photo-spectrometry. For brain tissue, this approach allows simultaneous measurements of rvCBF, srvO2, and rvHb. Ideally, alterations of CBF and oxygenation should be evaluated at various sections (arterial, capillary, venous) of vasculature. The approach to measure at the venous side of microcirculation seems to be rational as oxygen extraction fraction will increase in the case of cerebral tissue ischaemia. Furthermore, little is known on the effects of anaesthetic agents on human microcirculation. The technology is easy to set up, provides real-time data, and is even easy to use continuously during neurosurgery if the probe is not disturbing the site of surgery. However, the device has a number of significant limitations. The main one is that the device requires contact to the brain surface. Therefore, it is only applicable during craniotomies. Measurements may be influenced by neurosurgery, brain retraction, autonomic nerve system, cortical temperature, or \( \text{CO}_2 \) diffusion. Furthermore, the effect of Akrinor on cerebral measurement cannot be ruled out. The substance
had been given during normal and high propofol dosages to elevate arterial pressure acting by an increase in venous return and cardiac index. The mean thickness of the human grey matter is 2.5 mm; however, cortical thickness may vary (1–5 mm) in different brain regions.37 Furthermore, metabolism and flow significantly vary in different brain regions.22 Finding a macroscopically (avascular) healthy site for the probe placement is dependent on the size (>3 cm diameter) and location (supratentorial better than infratentorial) of craniotomy. In the case of bleeding during neurosurgery, the blood film on the cerebral cortex results in inaccurate measurement. The main disadvantage of laser-Doppler flowmetry is its non-quantitative measurement. Physiological variance and inaccuracy of measurements, especially at very low and very high values and also critical thresholds for pathophysiological states (e.g. cerebral ischaemia, hypoxia), are currently unknown for human cerebral tissue.

Conclusion

Combined laser-Doppler flowmetry and photo-spectrometry allows regional real-time measurement of human cerebral microcirculation (rvCBF, rvHb) and oxygen saturation (srvO2). An increase in propofol dosage [5.1 (2.3) mg kg\(^{-1}\) h\(^{-1}\), BIS 40 (9) vs 7.8 (2.1) mg kg\(^{-1}\) h\(^{-1}\), BIS 21 (7)] resulted in increased srvO2 in 2 mm (grey matter) cerebral depth without coupled reductions in rvCBF. Likewise, calculated parameters avDO\(_2\) and aCMRO2 decreased with an increase in propofol dosage. Unchanged rvHb levels indicate good filling of cerebral microvessels and adequate venous return of blood. In 8 mm (white matter) cerebral depth altered propofol dosage showed no effect on measured (vCBF, rvHb, srvO2) or calculated (avDO\(_2\), aCMRO2) parameters. These findings suggest that cerebral metabolic demand may be reduced by propofol administration in cortical regions; however, under alteration of the CBF/CMRO\(_2\) ratio.

Conflict of interest

There exists no financial relationship between any of the authors and LEA Medizintechnik GmbH (Giessen, Germany) or any other company or organization with potential or vested interest in the outcome of the study.

Funding

This study was supported by a Clinical Research Award (30 000 Euro) of the German Society of Anaesthesiology and Intensive Care Medicine (Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin e.V., DGAI, http://www.dgai.de).

References

1 Alkire MT, Haier RJ, Barker SJ, Shah NK, Wu JC, Kao YJ. Cerebral metabolism during propofol anaesthesia in humans studied with positron emission tomography. Anesthesiology 1995; 82: 393–403
21 Tsai AG, Johnson PC, Intaglietta M. Oxygen gradients in the microcirculation. Physiol Rev 2003; 83: 933–63
Human cerebral microcirculation and oxygen saturation

22 Ndubuizu O, LaManna JC. Brain tissue oxygen concentration measurements. Antioxid Redox Signal 2007; 9: 1207–19
23 Ivanov KP, Derry AN, Vovenko EP, Samoilov MO, Semionov DG. Direct measurements of oxygen tension at the surface of arterioles, capillaries and venules of the cerebral cortex. Pflugers Arch 1982; 393: 118–20
30 Alkire MT. Quantitative EEG correlations with brain glucose metabolic rate during anesthesia in volunteers. Anesthesiology 1998; 89: 323–33
31 Ludbrook GL, Visco E, Lam AM. Propofol: relation between brain concentrations, electroencephalogram, middle cerebral artery blood flow velocity, and cerebral oxygen extraction during induction of anesthesia. Anesthesiology 2002; 97: 1363–70