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

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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 ($srvO_2$) without reduction of capillary venous blood flow (rvCBF).
- Difference in oxygen content ($avDO_2$) and approximated cerebral metabolic rate of oxygen ($aCMRO_2$) decreased with an increase in propofol dosage in 2 mm cerebral depth.
- Alterations in BIS showed no effect on rvCBF, $srvO_2$, and haemoglobin amount (rvHb) or on $avDO_2$ or $aCMRO_2$ in 8 mm cerebral depth.
- These findings suggest that the $CBF/CMRO_2$ 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 ($srvO_2$), 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 ($avDO_2$) and cerebral metabolic rate of oxygen ($aCMRO_2$). Results: mean values (SD). Statistics: Mann–Whitney test (*$P<0.05$).

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 $srvO_2$ ($P=0.018$), and decreased $avDO_2$ ($P=0.025$) and $aCMRO_2$ ($P=0.022$), in 2 mm cerebral depth, while rvCBF and rvHb remained unchanged. In 8 mm cerebral depth, $srvO_2$, rvCBF, rvHb, and also calculated parameters $avDO_2$ and $aCMRO_2$ remained unaltered.

Conclusions. Findings suggest alteration of the $CBF/CMRO_2$ 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

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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 ($CMRO_2$) under maintenance of the coupled relationship between $CMRO_2$ and CBF.[1 2] However, there is some evidence that propofol also modulates the $CBF/CMRO_2$ ratio.[3] Studies in rats, hamsters, and pigs demonstrate that propofol induces generalized vasodilatation 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), vasodilatation 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 (O_2C-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 ($srvO_2$), and haemoglobin amount (rvHb) are determined in cerebral microcirculation using combined laser-Doppler flowmetry (rvCBF) and photospectrometry ($srvO_2$, rvHb). Additional measurement of arterial blood gas analysis allows for calculation of arteriovenous difference in oxygen content ($avDO_2$) and simultaneous measurements of rvCBF and $srvO_2$ allow

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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_2C-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 (Ultracover 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: CaO_2 (ml dl^{-1})=[1.39×Hb (g dl^{-1})×(Sa_{O_2} (%)/100)]+[Pa_{O_2} (mm Hg)×0.0034]. Venous partial pressure (Pv_{O_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: CvO_2 (ml dl^{-1})=[1.39×Hb (g dl^{-1})×($srvO_2$ (%)/100)]+[Pv_{O_2} (mm Hg)×0.0034]. The arteriovenous difference in oxygen content ($avDO_2$) was calculated using the formula: $avDO_2$ (ml dl^{-1})=CaO_2 (ml dl^{-1})−CvO_2 (ml dl^{-1}). Approximated cerebral metabolic rate of oxygen ($aCMRO_2$) was calculated using the formula: $aCMRO_2$ (arbitrary units)=[rvCBF (arbitrary units)/5]×$avDO_2$ (ml dl^{-1}). These data for $aCMRO_2$ (arbitrary units) were calculated using relative blood flow values (rvCBF). 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