

CLINICAL RESEARCH

The effect of propofol-sufentanil intravenous anesthesia on systemic and cerebral circulation, cerebral autoregulation and CO₂ reactivity: a case series



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Received 17 October 2019; accepted 2 April 2021

Available online 23 April 2021

KEYWORDS

Propofol;
Cerebral blood flow;
Cerebral
autoregulation;
CO₂-reactivity;
Applanation
tonometry;
Transcranial Doppler

Abstract

Background and objectives: The aim of our study was to assess systemic and cerebral hemodynamic changes as well as cerebral CO₂-reactivity during propofol anesthesia.

Methods: 27 patients undergoing general anesthesia were enrolled. Anesthesia was maintained using the Target-Controlled Infusion (TCI) method according to the Schnider model, effect site propofol concentration of 4 μg.mL⁻¹. Ventilatory settings (respiratory rate and tidal volume) were adjusted to reach and maintain 40, 35, and 30 mmHg EtCO₂ for 5 minutes, respectively. At the end of each period, transcranial Doppler and hemodynamic parameters using applanation tonometry were recorded.

Results: Systemic mean arterial pressure significantly decreased during anesthetic induction and remained unchanged during the entire study period. Central aortic and peripheral pulse pressure did not change significantly during anesthetic induction and maintenance, whereas augmentation index as marker of arterial stiffness significantly decreased during the anesthetic induction and remained stable at the time points when target CO₂ levels were reached. Both cerebral autoregulation and cerebral CO₂-reactivity was maintained during propofol anesthesia.

Conclusions: Propofol at clinically administered doses using the Total Intravenous Anesthesia (TIVA/TCI) technique decreases systemic blood pressure, but does not affect static cerebral autoregulation, flow-metabolism coupling and cerebrovascular CO₂ reactivity. According to our measurements, propofol may exert its systemic hemodynamic effect through venodilation.

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Trial registration: The study was registered at <http://www.clinicaltrials.gov>, identifier: NCT02203097, registration date: July 29, 2014.

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Introduction

Preserved cerebral autoregulation and CO₂-reactivity are key issues in neuroanesthesia. Propofol is recommended as an ideal anesthetic for neurosurgical procedures either as an induction agent or for maintenance as a part of Total Intravenous Anesthesia (TIVA).¹ Target-Controlled Infusion (TCI) technique allows for titration of the hypnotic effect during surgery along with rapid recovery after surgery,² making the drug attractive for neurosurgical practice. However, propofol has the drawback of decreasing systemic blood pressure,³ and thus challenging cerebral autoregulation especially in the induction phase. Especially in neuroanesthesia, the ideal anesthetic agent for maintenance should not have significant effect on cerebral autoregulation and CO₂-reactivity. In a different previous study using the same methodology we have proved that sevoflurane at Minimum Alveolar Concentration (MAC) < 1 meets these requirements.⁴

Although there are data indicating that propofol does not affect cerebral vasoreactivity to CO₂ and autoregulation is preserved during anesthesia with propofol,⁵ parallel data on the systemic and cerebral hemodynamic effects and their consequence on cerebral autoregulation and vasoreactivity using the TIVA/TCI technique are limited. Furthermore, the exact pathophysiological background of the systemic hypotension observed after induction with propofol is not known in all details from human studies.

During induction and maintenance of general anesthesia, a combination of different systemic and direct cerebral effects of the anesthetic agents has to be taken into account for the interpretation of the results. In fact, different studies assessed cerebral hemodynamic changes during intravenous propofol anesthesia but the interplay between systemic and cerebrovascular effects of the drug was not addressed.^{1,5} Thus, in the present study we aimed to assess changes in cerebral circulation and peripheral systemic hemodynamic changes in parallel during induction and maintenance of anesthesia with propofol using the TIVA/TCI technique.

Our aim was to assess the interplay between systemic and cerebrovascular effects of propofol. Additionally, we attempted to assess whether cerebral autoregulation is maintained at normocapnic steady state propofol and whether CO₂-reactivity of the cerebral circulation is affected by propofol.

Methods

Study population

After approval from the local Ethics Committee (DE RKEB/IKEB 4100-2014), written informed consent was

obtained from 30 ASA (American Society of Anesthesiologists) physical status I–II patients scheduled for elective varicectomy, inguinal hernioplasty, or breast surgery under general anesthesia. This was a case-series study. Exclusion criteria were severe cardiovascular disease, severe carotid artery stenosis, cerebrovascular disease, smoking, diabetes mellitus, renal disease, hyperlipidemia and left ventricular hypertrophy. The study was registered at <http://www.clinicaltrials.gov>, identifier: NCT02203097, registration date: July 29, 2014.

Devices and measurements

SphygmoCor (AtCor Medical, Sydney, Australia) device was used for applanation tonometry. The sensor was placed on the patient's skin over the radial artery. Under applanation of the radial artery, the transmural pressure of the radial artery wall is zero and the intraluminal applanation tonometry can be recorded by the sensor. The intraoperative use of the technique has been previously reported.^{6,7} In the present study parameters were recorded at the left radial artery. Systolic and diastolic aortic pressure, central aortic pulse pressure, peripheral pulse pressure, augmentation pressure, augmentation index normalized on actual heart rate (AIx[®]HR), and ejection duration were registered at predetermined phases of the study. All measurements were performed by the same experienced operator (DP).

Transcranial Doppler (TCD) measurements were performed using Rimed Digilite transcranial Doppler sonography (Rimed Ltd, Israel). The temporal acoustic window was used for assessing the middle cerebral artery. A fixed probe was used to register systolic, diastolic, and mean blood flow velocities at 45–55 mm depth; pulsatility indices were automatically calculated by the device.

Study protocol

Patients were premedicated with 100 mg diclofenac orally 60 minutes before anesthetic induction. Preoperative measurements were recorded one hour before anesthetic induction in supine position in quiet environment. Anesthesia was induced with a combination 2 µg.kg⁻¹ sufentanil bolus and propofol. Anesthesia was maintained using the TCI method according to the Schnider model, effect site concentration: 4 µg.mL⁻¹. Alaris Asena PK[™] (Cardinal Health, Alaris Products, Basingstoke, UK) TCI system was used for propofol administration. Intubation was facilitated by administration of 0.6 mg.kg⁻¹ rocuronium. Neuromuscular block was monitored with acceleromyograph (TOF Watch SX, NV Organon, Oss, the Netherlands). Standard monitoring included five-lead ECG, NIBP, BIS, and pulse oximetry. Normothermia was

maintained with forced-air system (Bair Hugger 750, 3M, Eden Prairie, MN, USA).

Patients were ventilated using volume-controlled square-wave flow pattern ventilation with 6–8 mL.kg⁻¹ Tidal Volume (TV), 5 cmH₂O PEEP, 2 L.min⁻¹ fresh gas flow and with a minute volume adjusted to reach and maintain 40 mmHg End-Tidal Carbon dioxide (EtCO₂) (Draeger Primus anesthesia workstation, Draeger Lübeck, Germany).

After induction of general anesthesia and intubation, lungs were ventilated in supine position for 20 minutes to reach EtCO₂ of 40 mmHg. At this stage, hemodynamic, transcranial Doppler, applanation tonometry, and ventilatory parameters (TV and breathing frequency) were simultaneously recorded.

In the second phase of the study minute ventilation (respiratory rate and tidal volume) was changed to reach and maintain 35 mmHg EtCO₂. After a 5-minutes stabilization period all measurements were repeated.

At the next stage of measurement series, ventilatory settings were changed to reach and maintain 30 mmHg EtCO₂. After a 5-minutes stabilization period, applanation tonometry and transcranial Doppler measurements were repeated. The flow chart of the study is summarized in Figure 1.

During each measurement, peripheral oxygen saturation (SpO₂), heart rate, systolic and diastolic blood pressure, systolic, diastolic, and mean blood flow velocities and pulsatility indices in the middle cerebral artery, systolic and diastolic aortic pressure, aortic pulse pressure, peripheral pulse pressure, augmentation pressure, augmentation index normalized on actual heart rate (Alx@HR), ejection duration, and operation index were registered.

Statistical methods

The normality of data distribution was tested by Shapiro-Wilks test. Differences were analyzed with the Repeated Measures Analysis of Variance (ANOVA) with Bonferroni post hoc correction. Values of $p < 0.05$ were accepted as statistically significant. Data are presented as mean (SD). MedCalc Statistical Software version 18.2.1. (MedCalc Software bvba, Ostend, Belgium) was used for statistical analysis. Spearman correlation analysis was used to assess the correlation between %–changes of MCAV and MAP values during induction.

Before starting the study, a power analysis was performed to calculate the necessary number of patients to be included. Our primary endpoint hypothesis was that propofol would not affect cerebral CO₂-reactivity. Based on a previous study⁸ we assumed that hyperventilation lasting for 1 minute results in a decrease of PCO₂ by 7 mmHg, accompanied by a 26.7 cm.s⁻¹ decrease of the middle cerebral artery mean blood flow velocity, that corresponds to a 3.84 cm.s⁻¹ change in blood flow velocity per 1 mmHg decrease of PCO₂. During our study we planned an overall 10 mmHg decrease (2 × 5 mmHg) in CO₂, we calculated with a 38.4 cm.s⁻¹ (30 cm.s⁻¹ standard deviation) change. Using a power of 0.9 and an alpha of 0.01, our calculation indicated that 12 patients need to be included to test our hypothesis. As both registration methods may be operator-dependent, for sake of clarity we decided to include 30 patients.

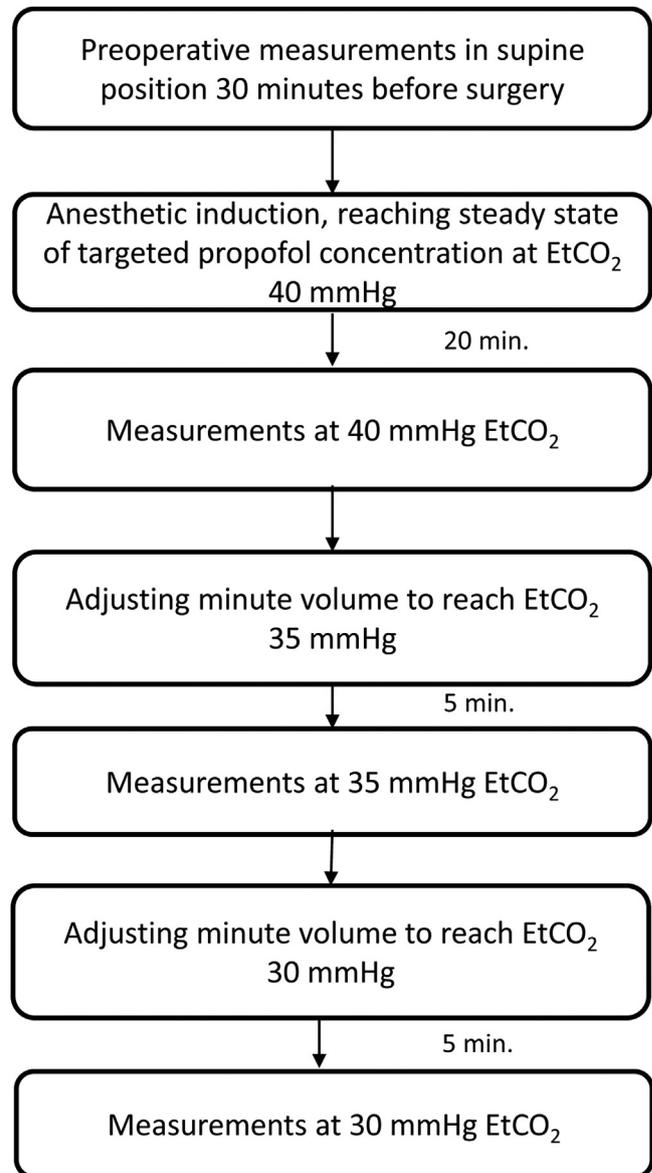


Figure 1 Flow chart of the study.

Results

Demographic data

Twenty-seven patients, aged 38 ± 9 years, 15 females, 12 males were enrolled. Their average height was 171.8 ± 10 cm, weight: 74.4 ± 20 kg, Body Mass Index (BMI): 24.8 ± 5 kg.m⁻². There were 9 patients with inguinal hiatal repair surgeries, 10 with breast surgeries, and 8 with varicectomies. Three patients were excluded due to inappropriate temporal window for transcranial Doppler.

Respiratory parameters during the procedure

During the study ventilatory settings were changed at different stages in order to reach and maintain different levels of EtCO₂ (40, 35, and 30 mmHg, respectively). Accordingly, we

Table 1 Hemodynamic and respiratory parameters during the course of the study.

| | Preop. | ETCO ₂ 40 | ETCO ₂ 35 | ETCO ₂ 30 | Time main effect <i>p</i> -value |
|---------------------------------|--------------|--------------------------|-------------------------|--------------------------|-------------------------------------|
| Systolic blood pressure (mmHg) | 124.8 (13.4) | 99.2 ^a (10.4) | 97.7 ^a (9.8) | 99.1 ^a (10.2) | <i>p</i> = 0.001 |
| Diastolic blood pressure (mmHg) | 81.2 (11.5) | 57.2 ^a (8.7) | 58.5 ^a (9.2) | 58.6 ^a (8.9) | <i>p</i> < 0.001 |
| Heart rate (1 min) | 68 (9.9) | 62 (9.4) | 60.3* (9.3) | 58.7* (8.2) | <i>p</i> = 0.05 |
| Tidal volume (mL) | n.a. | 460 (99) | 505 (95) | 530 (124) | <i>p</i> < 0.001 |
| Respiratory rate (1 min) | n.a. | 8.7 (1.1) | 11.8 (1.3) | 13.6 (1.7) | <i>p</i> < 0.001 |

Differences were analysed with the Repeated Measures Analysis of Variance (ANOVA) with Bonferroni post hoc correction.

Preop, Preoperative; ETCO₂, End-Tidal CO₂ at 40-35-30 mmHg.

^a Indicate differences compared to the baseline values.

* *p*=0.05.

observed significant differences in values of tidal volumes and respiratory rates (Table 1).

Hemodynamic parameters

Systolic blood pressure significantly decreased during anesthetic induction and remained unchanged in the course of the study. Diastolic blood pressure values showed a similar pattern. In contrast to this, no statistically significant changes have been observed in heart rate during anesthetic induction (Table 1).

Applanation tonometry parameters

Mean arterial pressure significantly decreased during induction of anesthesia and reaching the steady state and remained stable during the entire study. In contrast to this, aortic and peripheral pulse pressures did not change significantly during induction and reaching the target propofol concentration, and in the phases of the study (changes in PCO₂). A significant decrease has been observed in augmentation index during the induction of anesthesia and reaching the steady state with propofol but remained unchanged during CO₂-reactivity phases of the study (Fig. 2).

Transcranial doppler sonography parameters

Preoperative middle cerebral artery mean blood flow velocity values significantly decreased during induction of anesthesia under normocapnic conditions (EtCO₂ 40 mmHg). Mean blood flow velocity values significantly decreased further at EtCO₂ 35 and 30 mmHg. Pulsatility index values significantly increased during induction phase and they significantly increased along with the decreased EtCO₂ values (Fig. 3, panels a and b). There was a strong significant correlation between mean and EtCO₂ values (*p* < 0.001, Pearson's *r* = 0.79).

Relationship between mean arterial pressure and cerebral blood flow velocity changes after induction and stabilization of anesthesia

We assessed the percent change between mean arterial pressure and middle cerebral artery mean blood flow velocity before anesthetic induction and 20 minutes after

anesthesia was induced and a steady state of propofol anesthesia was reached at normocapnic PCO₂ (40 mmHg). At this normocapnic state, a significant linear relationship was found between percent change of mean arterial blood pressure and mean blood flow velocity, indicating preserved static cerebral autoregulation (Fig. 4).

Discussion

The most novel information of the present study is that during intravenous induction with propofol, the mean arterial pressure significantly decreased, but central aortic blood pressures and peripheral pulse pressures remained unchanged. This may indicate a venodilative effect of propofol as discussed below in detail.^{9,10} To our best knowledge, this is the first non-experimental observation referring to this effect of propofol in humans using noninvasive hemodynamic monitoring. As it decreases cerebral perfusion pressure, cerebral blood flow velocity significantly decreased in the middle cerebral artery during induction and this phenomenon was accompanied by an increase in pulsatility index, indicating vasoconstriction of the resistance vessels at the MCA territory. During the alteration of the systemic blood pressure, we also found a significant linear relationship between changes in systemic blood pressure and mean blood flow velocity in the middle cerebral artery (Fig. 5), indicating preserved static cerebral autoregulation.¹¹

Propofol decreases systemic blood pressure and cardiac output by approximately 30% and 40%, respectively.¹² A more recent study from De Wit et al. demonstrated that within the clinically administered dose range, cardiac output is not influenced by propofol, its main effect on the blood pressure is exerted through decreasing the tone of the venous capacitance vessels.³ Goodchild and Serrao reported on similar experimental observations: normal plasma concentrations of propofol do not have a negative inotropic effect but may cause relaxation of veins and increased capacitance without direct effect on arteries and arterioles at the periphery.¹³ A similar observation was published by Muzi et al. in humans.⁹ In our study we have also demonstrated an unchanged central aortic blood pressure and peripheral pulse pressure that may refer to an unaltered arterial resistance after propofol administration.

The mechanisms that are proposed for understanding the effect of propofol on cerebral circulation include the

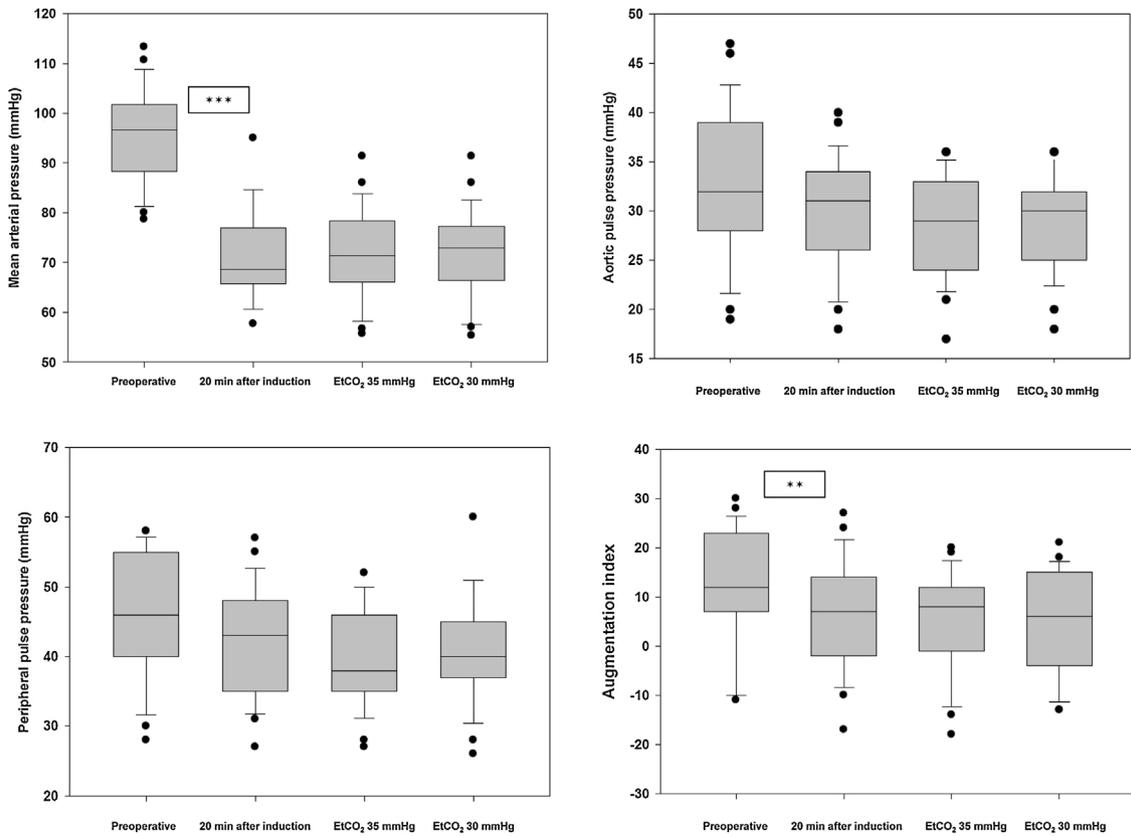


Figure 2 Applanation tonometry parameters at rest and during the course of the study. Medians and CI values are shown. **Indicates $p < 0.01$, ***Indicates $p < 0.001$ difference as compared to steady state values.

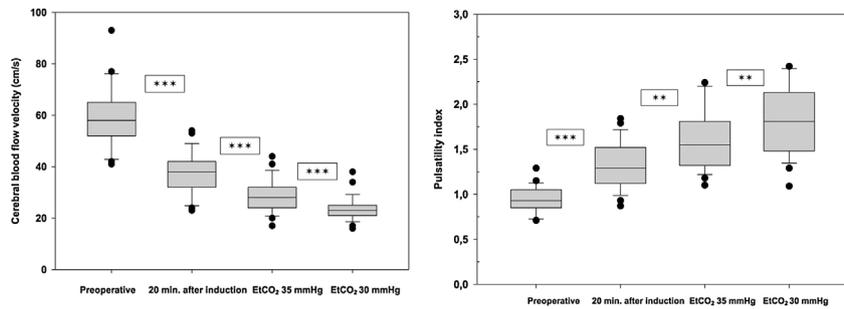


Figure 3 (a and b) Changes of middle cerebral artery mean blood flow velocity (panel a) and pulsatility index (panel b) during the course of the study. Medians and CI values are shown. **Indicates $p < 0.01$, ***Indicates $p < 0.001$ differences as compared to steady state values.

following components: a) Systemic hypotension challenging cerebral autoregulation by decreasing cerebral perfusion pressure, and b) The direct effect of propofol on the metabolism of the cerebral tissue. The interplay between these factors is summarized in Figure 5. It is conceivable that there is a balance between autoregulatory arteriolar vasodilation (as a consequence of decreased cerebral perfusion pressure) and arteriolar vasoconstriction (as a consequence of decreased $CMRO_2$) during propofol anesthesia. In previous studies it was observed that propofol decreases the metabolic rate of the cerebral tissue. One of the most important factors, is the decrease of the local CO_2 production as a consequence of the decreased metabolism.

Along with the decrease of local CO_2 production, a vasoconstriction of the resistance arterioles occurs. Based on the physiological mechanism of flow-metabolism coupling, if the metabolism of the cerebral tissue decreases, a vasoconstriction of the corresponding cerebral arterioles occurs in order to decrease the unnecessary hyperperfusion of the brain tissue. The effect of propofol on the cerebral circulation is thus a complex process: during propofol administration, global (and regional) cerebral blood flow decreases¹⁴⁻¹⁷ and it is counterbalanced by the decreased $CMRO_2$, ensuring preservation of the brain tissue metabolism.¹⁵

The relationship between arterial pressure of carbon dioxide and cerebral blood flow during general anesthesia

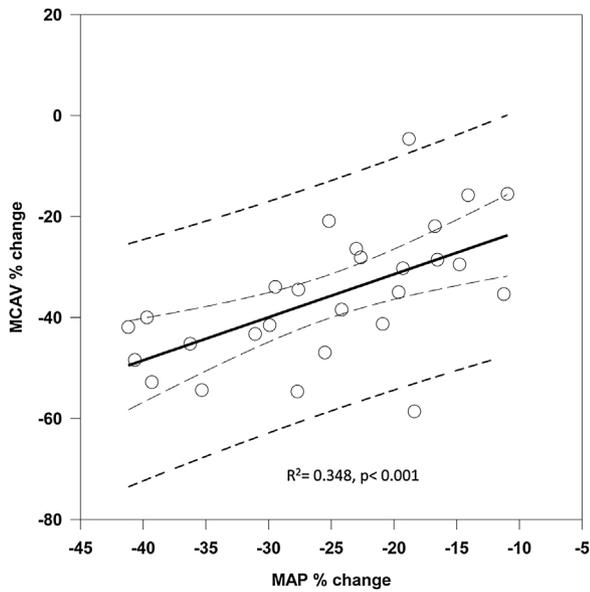


Figure 4 Spearman correlation between the %-change of Mean Arterial Pressure (MAP) and %-change of the Middle Cerebral Artery mean blood flow Velocity (MCAV) from baseline to anesthetic induction, reaching the steady state.

between the ranges of 30 to 50 mmHg CO₂ shows an exponential relationship.^{18,19} In previous volunteer studies, it has been demonstrated that forced hyperventilation lasting for

60 seconds results in a 38% percent decrease of the middle cerebral artery mean flow velocity compared to the resting Blood Flow Velocity (BFV).⁸ The normal values of cerebral vasoreactivity to CO₂ correspond to 1–2 mL/100 g/minutes/1 mmHg cerebral blood flow change or to a 2–5 cm.s⁻¹/ 1 mmHg cerebral blood flow velocity change.¹⁹ It has been shown previously that propofol at low doses (4–6 mg.kg⁻¹.h⁻¹) does not alter cerebral vasoreactivity.^{5,6,19} In accordance with these previous observations, in the present study, graded hypocapnia resulted in a 2 cm.s⁻¹/1 mmHg change in the cerebral blood flow velocity in the middle cerebral artery accompanied by an increased pulsatility index, indicating preserved hypocapnic vasoreactivity during propofol anesthesia.

Finally, we must mention the limitations of our study. First, although the number of cases meets the criteria of the predefined power analysis, it has to be noted that the results of a study performed in a limited number of low-risk patients undergoing minor surgical procedures may not be generalizable in clinical practice. The methodological limitations are that transcranial Doppler does not measure cerebral blood flow, only changes of the cerebral blood flow velocities are proportional to cerebral blood flow values. However, in a recent study it was demonstrated that there is a relationship between CBF and cerebral blood flow velocities during CO₂-reactivity measurements.¹⁸ Applanation tonometry was validated so far in a single clinical study during anesthesia that confirmed the feasibility of monitoring patient's afterload under general anesthesia from

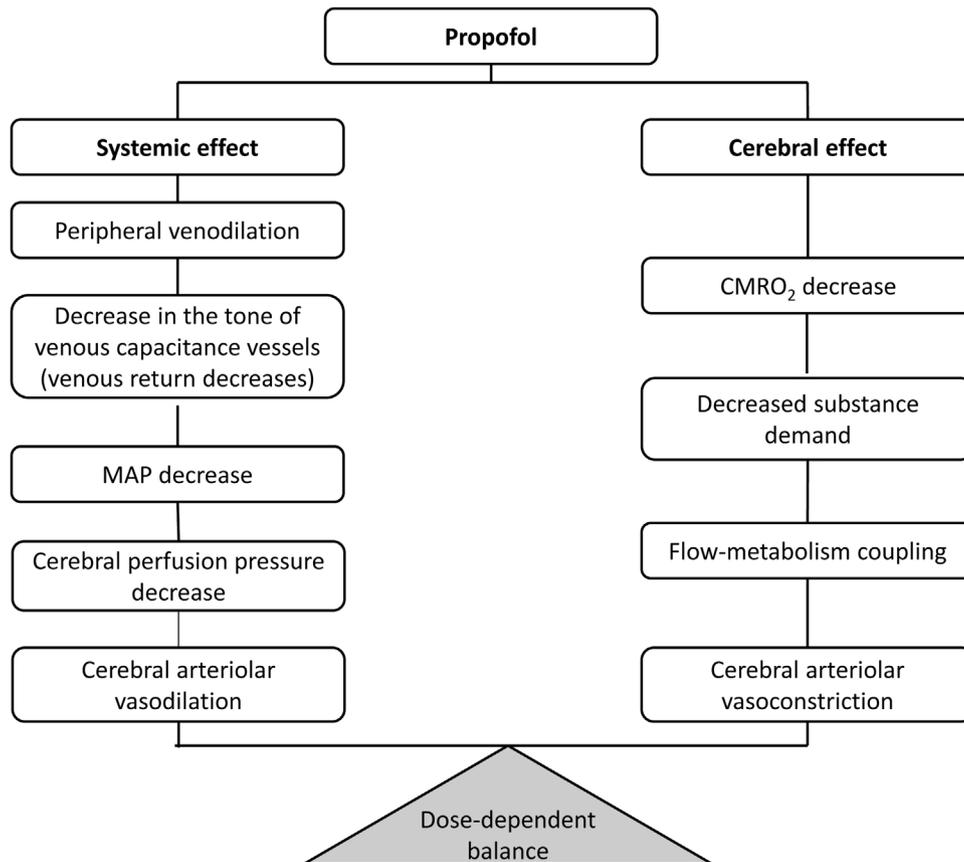


Figure 5 The proposed mechanism of action of propofol on cerebral blood flow regulation.

invasive pressure waveforms.⁷ In non-anesthetic validation studies, a good correlation was found between invasive and noninvasive indices, and slight underestimation of pressure values by applanation tonometry.²⁰ As we compared preanesthetic and intraoperative pressures in the same patients, we believe this did not influence our results. A further limitation to mention is that applanation tonometry is an operator-dependent procedure as is transcranial Doppler. Therefore, all measurements were performed by the same, experienced physician (DP and BF) in order to exclude operator-dependence.

In summary, propofol may exert its systemic hemodynamic effect through venodilation. At clinically administered doses using the TIVA/TCI technique, it decreases systemic blood pressure, but does not affect static cerebral autoregulation, flow-metabolism coupling and cerebrovascular CO₂ reactivity.

Availability of data and material

Data will be available upon request from the corresponding author.

Funding

The work was supported by the Hungarian Brain Research Program (grant number 2017-1.2.1-NKP-2017-00002), the founder is the Hungarian Academy of Sciences. Role: supporting central nervous system anesthesiology studies, CM, BF are supported to design, perform and interpreting studies assessing the effect of anesthetics of cerebral blood flow.

Conflicts of interest

The authors declare no conflicts of interest.

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