Effects of propofol on human microcirculation

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Background. It is increasingly believed that acute microvascular alterations may be involved in the development of organ dysfunction in critically ill patients. Propofol significantly decreases vascular tone and venous return, which can induce arterial hypotension. However, little is known about the microcirculatory effects of propofol in healthy humans.

Methods. We conducted a prospective, open-labelled trial in 15 patients anaesthetized by propofol for transvaginal oocyte retrieval. The sublingual microcirculatory network was studied before, during, and after propofol infusion using orthogonal polarization spectral imaging.

Results. Mean (sd) calculated propofol effect-site concentration was 6.5 (1.8) µg ml⁻¹. During propofol administration, systemic haemodynamic and oxygenation variables were unchanged, but total microvascular density decreased by 9.1% (P < 0.05). The venular density remained unchanged, but the density of perfused capillaries was significantly reduced by 16.7% (P < 0.05). Microcirculatory alterations resolved 3 h after discontinuation of the propofol infusion.

Conclusions. Propofol infusion for anaesthesia in man reduces capillary blood flow.


Keywords: blood, flow; oxygen, consumption; oxygen, tissue; oxygen, transport; tissue perfusion; pharmacology, propofol

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Propofol administration, at clinical doses, has significant haemodynamic effects. It has limited effects on the contractility of the heart, but induces arterial hypotension primarily by decreasing vascular tone and venous return. These effects are usually easily compensated by fluid administration, vasopressor agents, or both. In contrast to its systemic haemodynamic effects, little is known about the effects of propofol on the microcirculation. Acute microvascular alterations have been observed in patients with severe sepsis and in patients with severe cardiac failure, and these alterations are more severe in patients with a poor outcome. Experimental data suggest that an impaired microcirculation may lead to organ dysfunction, although this is difficult to prove in man, it may be justified to avoid the agents that could further worsen microvascular perfusion. Some anaesthetic agents have been shown to alter the microcirculation in experimental conditions, leading to impaired oxygen extraction capabilities. However, these effects may be specific to the anaesthetic agent, its dosage, and its route of administration. We hypothesized that anaesthesia with propofol may be associated with microvascular alterations.

We used the orthogonal polarization spectral (OPS) imaging technique (Fig. 1), a non-invasive method for assessing the microcirculatory blood flow in vivo in humans, to study the effects of propofol on the human microcirculation in patients undergoing transvaginal oocyte retrieval for assisted reproductive techniques.

Methods

After approval by the local research ethics committee and written informed consent, 15 ASA I adult women undergoing transvaginal oocyte retrieval for assisted reproductive techniques under general anaesthesia were enrolled. Patients with a full stomach, predicted difficulty in intubation and airway maintenance, and contraindications to laryngeal mask insertion were excluded. Patients with diabetes, hypertension, vascular disease, cirrhosis, chronic renal failure, and ovarian hyperstimulation syndrome were also excluded.

All patients underwent routine preoperative evaluation. Standard monitoring included ECG, non-invasive arterial pressure measurement, pulse oximetry, and capnography. External auditory canal temperature was intermittently
assessed using a digital thermometer. During induction, the lungs were ventilated with 100% oxygen via a facemask. Patients were anaesthetized with propofol (Diprivan 1%, AstraZeneca, Belgium), administered by target-controlled infusion (TCI), using ToolBox 4.8 software on a laptop computer controlling a Pilot Anaesthesia pump (Fresenius, Germany). The pharmacokinetic model used for propofol infusion has been described previously by Schnider and colleagues. Propofol TCI was used to induce and maintain anaesthesia, targeting both stable haemodynamics and absence of movement during oocyte retrieval. After induction, a non-lubricated laryngeal mask airway (size 3 or 4) was inserted and the lungs were ventilated using a 40% oxygen mixture. The tidal volume was set at 10 ml kg\(^{-1}\) and ventilatory frequency was adjusted to maintain the end-tidal CO\(_2\) between 4.4 and 4.9 kPa. At the end of the procedure, the propofol infusion was discontinued, breathing and haemodynamics were re-evaluated, and the patient was transferred to the post-anaesthesia care unit.

The OPS imaging technique has been described elsewhere. Briefly, light is reflected by a polarizing beam splitter and illuminates the target tissue perpendicular to the emitted light. The beam undergoes progressive reflection and scattering while travelling through the tissue. The reflected remitted light passes through a second polarizer and is processed by a video camera. More than 10 scattering events are necessary to depolarize the incident beam, thus only light remitted by deeper tissue layers passes the second polarizer. The reflected light scattered at or near the surface remains polarized and is eliminated by the second filter. As the wavelength is within the haemoglobin absorbance spectrum, images of the microcirculation are obtained by back-illumination from scattered depolarized light coming from deeper tissue layers. In contrast to intravital fluorescence microscopy, vessel walls are not visible, thus vessels are only visualized when containing red blood cells.

The Cytoscan ARII (Cytometrics, Philadelphia, PA, USA) was used to study the sublingual microcirculation. After removing oral secretions, we gently applied the device on the lateral side of the tongue. During each assessment, five sequences from different adjacent areas were recorded (technical quality required: minimum length 10 s, absence of motion-related artifacts, and absence of saliva film) and stored under a random number on a hard disk for further analysis. The data were later analysed by the investigator (M.K.) blinded to the origin of the images, according to the semi-quantitative method described by De Backer and colleagues. Briefly, each investigated area was divided by three equidistant horizontal and three equidistant vertical lines. Vessel density was defined as the number of vessels crossing these lines divided by the total length of the lines. Blood flow was defined as continuous, intermittent, or absent. The vessels were separated into large vessels (mainly venules) and small vessels (mainly capillaries) using a cut-off value of 20 \(\mu\)m. The proportion of perfused vessels was calculated as follows: \(100 \times \frac{\text{total number of vessels} - \text{(no flow + intermittent flow)}}{\text{total number of vessels}}\). The perfused vessel density was calculated by multiplying vessel density by the proportion of perfused vessels (of note, vessels containing no red blood cells are not included in this calculation).
each patient, and at each assessment, the data of the five areas were averaged. We have previously reported that intra-observer variability is smaller than 5% for most measurements,\textsuperscript{10} thus changes of more than 10% were considered as statistically significant. Microvideoendoscopic measurements were obtained before induction, 15 min after induction, and 3 h after the end of the propofol infusion. During propofol administration, the microcirculation was assessed after obtaining steady-state anaesthesia (effect-site concentration=plasma concentration); no change in the target concentration was allowed during this period.

After confirmation of normal distribution by a Kolmogorov–Smirnov test, analysis of variance for repeated measures was used followed by a least significant difference test for pair-wise post hoc comparisons (SPSS\textsuperscript{11} software, SPSS Inc., USA). Results are expressed as mean (SD). \(P<0.05\) was considered significant.

**Results**

The 15 patients had a mean (range) age of 35 (25–41) yr. During the assessment of the microcirculation, the mean calculated propofol effect-site concentration was 6.5 (1.8) \(\mu\text{g}\text{ml}^{-1}\) (range 4.5–10 \(\mu\text{g}\text{ml}^{-1}\)). There were no significant changes in heart rate or \(S_R\), but body temperature decreased during anaesthesia and the arterial pressure decreased at the end of the intervention (Table 1).

Approximately 18\,000 vessels were assessed by microvideoendoscopy. Table 2 shows the microvascular changes. Propofol infusion significantly decreased total microvascular density (relative change: \(-9.1\%, P<0.05\)). It did not affect the total large vessel density and flow remained continuous in more than 99% of large vessels during the three evaluation periods. Propofol infusion induced a significant reduction in total small vessel density (relative change: \(-12.7\%, P<0.05\)). Although not significant, the proportion of small vessels containing red blood cells with intermittent or no flow increased, decreasing further the density of continuously perfused small vessels (relative change: \(-16.7\%, P<0.05\)).

**Discussion**

This is the first study to investigate the microcirculatory effects of propofol by direct visualization of the human microcirculation using OPS imaging. Most of the experimental studies investigating the microcirculatory effects of i.v. anaesthetics used intravital microscopy. However, this technique cannot be used in humans, as it requires surgical tissue preparation, large microscopes, and fluorescent dye infusion.\textsuperscript{23} OPS imaging has been validated against intravital fluorescence microscopy in both experimental and human models.\textsuperscript{24,25} In healthy humans, OPS imaging provides better image quality than conventional capillary microscopy.\textsuperscript{26} We elected to study young, healthy humans, in whom covariables were unlikely to interfere with the results. Anaesthetic concentrations of propofol induced moderate and reversible alterations in microcirculatory blood flow. There was a marked reduction in total small vessel density, indicating completely collapsed vessels, as the OPS technique allows only visualization of vessels containing red blood cells. The small increase in non-perfused and intermittently perfused small vessels suggests an increase in microvascular blood flow heterogeneity, contributing to a reduction in oxygen extraction capabilities.\textsuperscript{20} This observation is in line with previous data in dogs reporting that propofol alters oxygen extraction capabilities.\textsuperscript{18} It is important to note that capillaries account for a large majority of the observed small vessels. Thus, our results show that propofol directly affects capillary blood flow. In contrast, venular blood flow was not altered by propofol as large vessel density remained unchanged and intermittent or stopped flow was observed in <1% of large vessels.

Interestingly, the observations that the large vessel density remains unaltered during microcirculatory dysfunction are similar to those made during acute disease processes.\textsuperscript{10,12} Indeed, large vessels observed by OPS mainly represent venules, which, in contrast to capillaries, constitute a non-recruitable passive drainage network. Incidentally, our 99% Table 1 Clinical data of the 15 patients. BIS, bispectral index; mean (sd); \(*P<0.05\) compared with baseline and during propofol infusion; \(\dagger P<0.05\) compared with baseline and after propofol

<table>
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<tr>
<th></th>
<th>Baseline</th>
<th>During propofol</th>
<th>After propofol</th>
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<tr>
<td>Arterial pressure (mm Hg)</td>
<td>89 (9)</td>
<td>90 (14)</td>
<td>77 (9)(\dagger)</td>
</tr>
<tr>
<td>Heart rate (beats min(^{-1}))</td>
<td>79 (12)</td>
<td>84 (15)</td>
<td>74 (8)</td>
</tr>
<tr>
<td>(S_R), (%)</td>
<td>98.1 (1.1)</td>
<td>98.7 (0.6)</td>
<td>NA</td>
</tr>
<tr>
<td>End-tidal CO(_2) (kPa)</td>
<td>NA</td>
<td>4.6 (0.1)</td>
<td>NA</td>
</tr>
<tr>
<td>BIS index</td>
<td>NA</td>
<td>26.9 (6.5)</td>
<td>NA</td>
</tr>
<tr>
<td>Temperature ((^\circ)C)</td>
<td>36.4 (0.2)</td>
<td>35.9 (0.2)(\dagger)</td>
<td>36.6 (0.4)</td>
</tr>
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Table 2 Effects of propofol on vessel density. In addition to mean (sd) changes to baseline in density, relative changes are also shown (%). The vessels were separated into large and small vessels using a cut-off value of 20 \(\mu\)m. The proportion of perfused vessels was calculated as follows: 100\(\times\)(total number of vessels−(no flow+intermittent flow))/total number of vessels. The perfused vessel density was calculated by multiplying vessel density by the proportion of perfused vessels. \(*P<0.05\) compared with baseline

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<th>Baseline</th>
<th>During propofol</th>
<th>After propofol</th>
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<tr>
<td>Total vascular density ((n \text{mm}^{-1}))</td>
<td>10.6 (0.9)</td>
<td>9.7 (0.8)*(\dagger)</td>
<td>(9.1)</td>
</tr>
<tr>
<td>Large vessel density ((n \text{mm}^{-1}))</td>
<td>3.2 (0.5)</td>
<td>3.2 (0.6) (0.0)</td>
<td>3.0 (0.6)(\dagger)</td>
</tr>
<tr>
<td>Proportion of perfused large vessels (%)</td>
<td>99.4</td>
<td>99.2</td>
<td>99.7</td>
</tr>
<tr>
<td>Perfused large vessel density ((n \text{mm}^{-1}))</td>
<td>3.2 (0.4)</td>
<td>3.1 (0.6) (1.0)</td>
<td>3.0 (0.6) (1.0)</td>
</tr>
<tr>
<td>Small vessel density ((n \text{mm}^{-1}))</td>
<td>7.4 (0.2)</td>
<td>6.5 (0.2)*(\dagger)</td>
<td>7.2 (0.4) (3.7)</td>
</tr>
<tr>
<td>Proportion of perfused small vessels (%)</td>
<td>92.7</td>
<td>88.9</td>
<td>92.8</td>
</tr>
<tr>
<td>Perfused small vessel density ((n \text{mm}^{-1}))</td>
<td>6.9 (0.8)</td>
<td>5.8 (0.8)*(\dagger)</td>
<td>6.6 (1.5) (3.7)</td>
</tr>
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venular perfusion rate demonstrates acceptable probe handling, as excessive probe-induced external pressure may provoke microvascular collapse and false-positive perfusion defects.22

To our knowledge, no previous study has investigated the effects of propofol on the terminal microcirculation in humans. Experimental studies have indicated that propofol administration induces generalized vasodilatation throughout the arteriolar tree.15–17 Selective vasodilatation of terminal arterioles may improve oxygen delivery when blood flow is limited, whereas excessive and non-discriminating vasodilatation might induce a distributive defect with shunting of blood.27 However, the effects of this arteriolar vasodilatation on downstream capillary blood flow have been poorly investigated. In a dog model of haemorrhagic shock, Van der Linden and colleagues18 reported a dose-dependent increase in critical oxygen delivery during propofol anaesthesia, reflecting an impairment in oxygen extraction capabilities. These results18 strongly suggest a propofol-induced alteration of microcirculatory regulation and blood flow. Using a local hydrogen clearance technique, Gustafsson and colleagues28 showed that, compared with ketamine and pentobarbital, capillary blood flow was reduced most by propofol, both at baseline and during haemorrhage. Flow distribution, as assessed by the percentage of zero capillary flow, was more pronounced in the propofol group, even at baseline. These results are in accordance with our present study, showing an increase of capillaries with intermittent or no flow during propofol infusion. Finally, in animals anaesthetized with propofol, Brookes and colleagues29 observed a reduction in rat mesenteric capillary diameter during haemorrhage, reflecting reduced capillary blood flow as changes in capillary diameter are passive, depending on upstream changes in blood flow. Though neither of these experimental studies28 29 compared capillary blood flow before and during propofol anaesthesia, they both demonstrated that microcirculatory blood flow was affected more by propofol than by other i.v. anaesthetics, both during steady-state anaesthesia and during haemorrhage, thus tending to support our results. Only one previous study has addressed the issue of propofol-induced changes in the microvasculature in humans. Using venous congestion plethysmography, Bruegger and colleagues30 reported no significant change in the capillary filtration coefficient, an index of microvascular permeability, during propofol anaesthesia.

One should consider that the decrease in microvascular perfusion could be due to other factors, including changes in core temperature, $P_{acO_2}$, or $P_{aeO_2}$, insertion of the laryngeal mask airway or surgical stress, rather than to a direct propofol-mediated vasoactive effect. Profound hypothermia reduces oxygen consumption and local cooling to 8°C of a hamster dorsal skinfold preparation was associated with a 30% decrease in functional capillary density and a drastic increase in no-flow capillaries (from 0.5% to 44% of total capillaries).31 In our study, it seems unlikely that the observed 0.7°C decrease in temperature played any significant role. Variations in $P_{acO_2}$ may also influence the circulation; however, end-tidal $CO_2$ was maintained at 4.6 kPa during mechanical ventilation, so that normocapnia can be assumed in our young ASA I patients. Hyperoxia has been shown to decrease functional capillary density in experimental conditions,32 although these observations have usually been made using an $FiO_2$ of 1.0 and the effects of oxygen are generally observed only at very high $P_{O_2}$ values.33 Nevertheless, we cannot exclude that mild hyperoxia may have contributed to our results. Lingual blood flow may be altered during laryngeal mask airway management, but this is usually due to direct mechanical compression of either the dorsal lingual or the deep lingual vein. However, obstruction of the venous drainage of the tongue should induce intermittent and no-flow patterns, similar to local probe-induced compression. The 99% venular perfusion rate reasonably eliminates the possibility of laryngeal mask-induced microvascular perfusion changes. Finally, increased sympathetic outflow may influence the microcirculation; oocyte retrieval is, however, a minor procedure and heart rate changes do not indicate a major change in sympathetic activity during the harvesting. In our institution, patients regularly undergo oocyte retrieval procedures using exclusively propofol-based anaesthesia.

One cannot separate the microvascular effects of propofol from those of the lipid emulsion used. Indeed, in an experimental setting, similar vasodilatory effects were observed during administration of the commercially available propofol emulsion and during infusion of Intralipid.8–15 Nevertheless, even though the distinction would be interesting from a pathophysiological point of view, it is clinically irrelevant, as both compounds are administered together.

We used a semi-quantitative approach to estimate vessel density and flow. OPS imagery does not allow identical vessels to be examined over time and estimation of blood flow and blood cell velocity remains hazardous as OPS provides a two-dimensional projection of the threedimensional microvascular network. Unfortunately, other techniques do not perform better, as laser Doppler flowmetry averages the velocities in all explored vessels and does not take into account heterogeneity of blood flow. Our study assessed only the sublingual region, which is easily accessible in the operating theatre. Microcirculatory sublingual blood flow seems to be highly representative of the splanchnic microcirculation, which is of particular interest in the critically ill patient. Both regions share the same embryogenic origin and several investigators have reported good correlation between gastric $PCO_2$ gap, sublingual $PCO_2$ gap, and OPS assessed microcirculation.34–36 In experimental conditions, microcirculatory alterations were reported to be similar in the buccal area and in the gut.37

Finally, one may argue that these microcirculatory changes had no significant consequences on organ
function in these otherwise healthy women. It is true that the microcirculation was relatively preserved during propofol administration, despite a significant decrease in microvascular perfusion. In patients with more severe microvascular alterations to begin with, administration of propofol may induce additional alterations with important consequences on organ function. In patients with septic shock, Sakr and colleagues reported that survivors were able to improve their capillary perfusion by 8% (absolute change) within the first 24 h of the onset of shock. It may, therefore, appear wise to avoid factors that could handicap the capacity of microvascular alterations to heal.

In summary, a short-term infusion of propofol reduces microcirculatory perfusion in young, healthy females. Further research is warranted to explore microcirculatory changes during anaesthesia and sedation in the critically ill patient.

Funding

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