The effect of propofol on haemodynamics: cardiac output, venous return, mean systemic filling pressure, and vascular resistances†

F. de Wit1,*, A. L. van Vliet2, R. B. de Wilde3, J. R. Jansen3, J. Vuyk1, L. P. Aarts1, E. de Jonge3, D. P. Veelo4 and B. F. Geerts1,4

1Department of Anaesthesiology, Leiden University Medical Centre, Leiden, The Netherlands, 2Department of Anaesthesiology, Alrijne Hospital, Leiderdorp, The Netherlands, 3Department of Intensive Care, Leiden University Medical Centre, Leiden, The Netherlands, and 4Department of Anaesthesiology, Academic Medical Centre, Amsterdam, The Netherlands

*Corresponding author. E-mail: fdewit@lumc.nl

Abstract

Background: Although arterial hypotension occurs frequently with propofol use in humans, its effects on intravascular volume and vascular capacitance are uncertain. We hypothesized that propofol decreases vascular capacitance and therefore decreases stressed volume.

Methods: Cardiac output (CO) was measured using Modellflow® in 17 adult subjects after upper abdominal surgery. Mean systemic filling pressure (MSFP) and vascular resistances were calculated using venous return curves constructed by measuring steady-state arterial and venous pressures and CO during inspiratory hold manoeuvres at increasing plateau pressures. Measurements were performed at three incremental levels of targeted blood propofol concentrations.

Results: Mean blood propofol concentrations for the three targeted levels were 3.0, 4.5, and 6.5 µg ml⁻¹. Mean arterial pressure, central venous pressure, MSFP, venous return pressure, Rv, systemic arterial resistance, and resistance of the systemic circulation decreased, stroke volume variation increased, and CO was not significantly different as propofol concentration increased.

Conclusions: An increase in propofol concentration within the therapeutic range causes a decrease in vascular stressed volume without a change in CO. The absence of an effect of propofol on CO can be explained by the balance between the decrease in effective, or stressed, volume (as determined by MSFP), the decrease in resistance for venous return, and slightly improved heart function.

Clinical trial registration: Netherlands Trial Register: NTR2486.

Key words: anaesthetics, intravenous; cardiac output; propofol; vascular capacitance

Propofol, one of the most widely used i.v. hypnotic drugs, is used for induction and maintenance of general anaesthesia, procedural sedation, and sedation in the intensive care unit. Its rapid onset, fast recovery, and low rate of nausea and vomiting make propofol the sedative drug of choice in many situations. Use of propofol is, however, accompanied by a decrease in arterial blood pressure and systemic vascular resistance.2–5 The effect of propofol on cardiac output (CO) is uncertain, with reports varying from no effect6 to a significant decrease.3,5,7 Venodilation is an important component of the decrease in systemic vascular
resistance, as shown, for example, in a study measuring forearm venous venous compliance. Nonetheless, the effects of propofol on intravascular volume and vascular capacitance have not yet been explored in humans.

Recently, a method was described to measure mean systemic filling pressure (MSFP) in patients with intact circulation after cardiothoracic surgery. The MSFP is the pressure that exists in the systemic circulation during a no-flow state. It reflects the distending pressure generated by stressed volume (the volume that stresses the vessel walls, thus generating pressure). Given that MSFP is equal to capillary pressure, it is the driving pressure in venous return, and it allows calculation of the arterial and venous components of systemic vascular resistance. Venous return is equal to the difference between MSFP and central venous pressure (CVP) divided by the venous resistance.

We determined the MSFP in humans to gain a better understanding of the contribution of changes in intravascular volume and vascular capacitance to the haemodynamic effects of propofol. Based on previous studies, we hypothesized that propofol decreases vascular capacitance and therefore decreases stressed volume.

Methods

Patients

Seventeen postsurgical patients after elective open oesophageal resection or pancreaticoduodenectomy were enrolled after approval by the Leiden University medical ethics committee (reference P10.067) and registration at the Netherlands Trial Register (reference NTR2486). Informed consent was obtained at least 1 day before surgery. Patients with symptomatic peripheral vascular disease or pulmonary disease, aberrant cardiovascular anatomy, significant valvular regurgitation, or severe arrhythmias were excluded.

Before surgery, an epidural catheter was inserted, but local anaesthetics were not administered until after termination of the study. General anaesthesia was induced with target-controlled infusion (TCI) of propofol (Marsh model using a Module DPS Orchestra pump on a Primea IS base, Fresenius Vial, Brézins, France), continuous infusion of remifentanil, and bolus administration of atracurium or rocuronium, according to hospital standards. During surgery, a central venous catheter was inserted under ultrasound guidance, and an arterial catheter was inserted in the radial artery. The patient’s lungs were mechanically ventilated in a volume-controlled mode adjusted to achieve normocapnia with tidal volumes of 8–10 ml kg⁻¹ and a respiratory rate of 12–14 breaths min⁻¹. The fraction of inspired oxygen (FIO₂) was maintained at 0.4, and a PEEP of 5 cm H₂O was applied. Haemodynamic stability was achieved using fluids (normal saline and lactated Ringer’s solutions) and catecholamines (ephedrine, norepinephrine).

Measurements

Systemic arterial blood pressure (Pₐ) was monitored via a 20 gauge, 3.8 cm radial arterial catheter connected to a pressure transducer (PX600P, Edwards Lifesciences, Irvine, CA, USA). Central venous pressure was measured with a catheter inserted through the right internal jugular vein (MultiCath 3 venous catheter, Vigon GmbH & Co., Aachen, Germany) connected to a pressure transducer. The catheter tip position was checked with a chest radiograph. Both transducers were referenced to the intersection of the anterior axillary line and the fifth intercostal space. Airway pressure (Pₐvent) was measured at the entrance of the tracheal tube. Standard ECC leads were used to monitor heart rate (HR). Cerebral activity was measured using bispectral index (BIS®, Model A 2000, Aspect Medical Systems, Natick, MA, USA). Beat-to-beat cardiac output was obtained by Modelflow® (CO) pulse contour analysis (BMEYE, Amsterdam, The Netherlands) as previously described. Measurements were recorded for offline analysis at a sample frequency of 100 Hz and 0.2 mm Hg resolution.

Venous return curves were constructed by measuring steady-state Pₐ, CVP and CO throughout the final 3 s for a set of four 12 s inspiratory hold manoeuvres at increasing Pₐvent plateau pressures of 5, 15, 25, and 35 cm H₂O. The inspiratory hold manoeuvres were separated by 1 min intervals to re-establish baseline haemodynamic steady state. The CVP increases with the increase of Pₐvent, whereas CO and Pₐ decrease to reach a steady state between 7 and 12 s after initiation of inspiratory hold (Fig. 1). From the steady-state values of CVP and CO during the four inspiratory hold periods, a venous return curve was constructed using linear regression. The inspiratory hold manoeuvres were performed during three sequential, increasing target blood propofol concentrations (propofol Cₐ), depending on what was haemodynamically (i.e. arterial hypotension) feasible in the individual patient. Haemodynamic measurements were made only after propofol blood-effect site equilibration. Venous propofol blood concentration was determined after collecting samples into test tubes containing potassium oxalate at 6 min after a predicted target propofol concentration had been achieved, and analysed as described.

Data analysis and statistics

The CVP and CO data were fitted by linear regression using a least-squares method for each volume state to define the venous return curve. We defined MSFP by extrapolation to zero flow, assuming that airway pressure does not affect MSFP. We have previously validated this extrapolation in piglets and described the technique in postoperative cardiac surgery patients. Total systemic vascular resistance (Rsys) was calculated as the ratio of the pressure difference between mean Pₐ and mean CVP and CO, as follows:

\[ R_{sys} = \frac{P_a - CVP}{CO} \]

The resistance downstream to MSFP was taken to reflect the resistance to venous return (Rv) and was calculated as the ratio of the pressure difference between MSFP and CVP and CO, as follows:

\[ R_v = \frac{MSFP - CVP}{CO} \]

Systemic arterial resistance (Ra) was taken to be the difference between systemic and venous resistance. The pressure gradient
to venous return \( (P_{vr}) \) was defined as the pressure difference between MSFP and CVP.

After confirming a normal distribution of data with the Kolmogorov–Smirnov test, differences in parameters between different propofol concentrations were analysed using Student’s paired t-tests, with \( P < 0.05 \) considered significant. All values are given as the mean (SD).

**Results**

Seventeen patients, three women and 14 men, were enrolled. Mean age was 62 (9) yr (range 42–79 yr), mean weight 84 (12) kg, mean height 180 (8) cm and mean body mass index 26 (2.7) kg m\(^{-2}\). All subjects underwent oesophageal resection, except one subject who underwent pancreaticoduodenectomy. One subject was given a low dose of norepinephrine (0.02 µg kg\(^{-1}\) min\(^{-1}\)) during the entire study interval; all other subjects did not receive vasoactive medication. Subjects had a mean positive fluid balance of 1.85 (1.07) litres (range 0.6–3.8 litres).

Pooled measurements obtained at three increasing propofol concentrations are reported in Table 1. Mean propofol \( C_b \) were 3.0 (0.9), 4.5 (1.0), and 6.5 (1.2) µg ml\(^{-1}\). The BIS decreased with increasing propofol \( C_b \) to 54 (13), 39 (8), and 29 (7), respectively. Increasing concentrations of propofol led to venous dilatation as venous resistance decreased. Arterial resistance decreased in a similar manner, because the ratio between \( R_a \) and \( R_{vr} \) did not change significantly. Mean arterial pressure decreased from 82 (12) to 75 (12) and 66 (10) mm Hg, respectively, at the three propofol \( C_b \) levels (\( P < 0.001 \)). A small but significant increase in HR was found as propofol \( C_b \) increased [69 (10), 71 (12), and 73 (11) beats min\(^{-1}\), respectively; \( P < 0.001 \)]. Pulse pressure variation increased from 7 (3) to 7 (3) to 11 (5)%, at increasing blood propofol levels (\( P < 0.001 \)). The MSFP decreased significantly with the increase in propofol \( C_b \) (Fig. 2). The pressure to venous return (MSFP minus CVP) also decreased, but there is no change, resulting in no significant change. Therefore, CO did not change significantly despite the increased propofol \( C_b \).

**Discussion**

We showed that an increase in propofol \( C_b \) is associated with a decrease in systemic arterial pressure without a significant change in CO. Venous and total peripheral resistance and MSFP decline with increasing propofol \( C_b \).

Figure 3 shows a venous return curve plotted using the average values of CVP, MSFP, and CO. With increasing propofol concentrations, the venous return curve turns clockwise, which
is indicated by the decrease in MSFP and the constant value of CO at a CVP of zero. The steeper curve indicates a decrease in \( R_{\text{vr}} \), as the slope of the curve equals \( 1/R_{\text{vr}} \).

The decrease in MSFP can be explained by either an increase in systemic vascular compliance or an increase in unstressed volume (the volume in the circulation that does not build up intravascular pressure). Several studies have explored the effect of propofol on the venous circulation. Muzi and colleagues\(^8\) showed a significant increase in forearm venous compliance by occlusive plethysmography during propofol administration. Robinson and colleagues\(^18\) later showed that the effects on forearm venous compliance were similar to the effects of sympathetic denervation by stellate ganglion block. Hoka and colleagues\(^19\) examined the effect of propofol on vascular stressed volume in rats by measuring MSFP. They also showed a dose-dependent decrease in MSFP, but not in rats whose sympathetic nervous system was blocked with hexamethonium, which suggested a propofol-induced inhibition of the sympathetic nervous system. Given that a change in sympathetic activity mainly causes an alteration of stressed volume and not of venous compliance, this also seems to be the case with propofol infusion.

The intersection of a cardiac function curve with the venous return curve reflects steady-state CO (Fig. 4). The increase in SVV at higher propofol concentrations means that the cardiac function curve is steeper at higher propofol concentrations. As our data also show that CO remains constant and CVP decreases, this suggests a change in the cardiac function curve. This small enhancement

### Table 1  
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Propofol concentration 1 (low)</th>
<th>Propofol concentration 2 (middle)</th>
<th>Propofol concentration 3 (high)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>Mean 82, sd 13</td>
<td>Mean 75, sd 12, ( P_1 = 0.04 )</td>
<td>Mean 66, sd 10, ( P_2 &lt; 0.001 )</td>
</tr>
<tr>
<td>HR (beats min(^{-1}))</td>
<td>69, sd 10</td>
<td>71, sd 12, ( P_1 = 0.047 )</td>
<td>73, sd 11, ( P_2 &lt; 0.001 )</td>
</tr>
<tr>
<td>CO (litre min(^{-1}))</td>
<td>5.7, sd 1.2</td>
<td>5.8, sd 1.1, ( P_1 = 0.01 )</td>
<td>5.5, sd 1.2, ( P_2 = 0.34 )</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>7.8, sd 2.8</td>
<td>7.3, sd 2.9, ( P_1 = 0.04 )</td>
<td>7.2, sd 3.0, ( P_2 = 0.03 )</td>
</tr>
<tr>
<td>MSFP (mm Hg)</td>
<td>27.9, sd 5.4</td>
<td>24.6, sd 4.9, ( P_1 = 0.01 )</td>
<td>21.4, sd 4.2, ( P_2 &lt; 0.001 )</td>
</tr>
<tr>
<td>VR slope (litre min(^{-1}) mm Hg(^{-1}))</td>
<td>(-0.31, sd 0.11)</td>
<td>(-0.30, sd 0.21, P_1 = 0.41)</td>
<td>(-0.40, sd 0.10, P_2 &lt; 0.001)</td>
</tr>
<tr>
<td>( R_{\text{vr}} ) (mm Hg min litre(^{-1}))</td>
<td>20.2, sd 5.6</td>
<td>17.2, sd 5.1, ( P_1 = 0.01 )</td>
<td>14.2, sd 3.4, ( P_2 &lt; 0.001 )</td>
</tr>
<tr>
<td>( R_{\text{sys}} ) (mm Hg min litre(^{-1}))</td>
<td>8.6, sd 3.4</td>
<td>7.5, sd 2.6, ( P_1 = 0.054 )</td>
<td>5.8, sd 2.2, ( P_2 &lt; 0.001 )</td>
</tr>
<tr>
<td>( R_{\text{sys}}/R_{\text{sys}} )</td>
<td>13.6, sd 4.5</td>
<td>12.1, sd 4.3, ( P_1 = 0.004 )</td>
<td>11.0, sd 3.6, ( P_2 = 0.002 )</td>
</tr>
<tr>
<td>SVV (%)</td>
<td>6.6, sd 2.2</td>
<td>7.1, sd 2.9, ( P_1 = 0.48 )</td>
<td>9.7, sd 3.9, ( P_2 = 0.002 )</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>7.0, sd 2.9</td>
<td>7.5, sd 2.8, ( P_1 = 0.45 )</td>
<td>10.8, sd 4.7, ( P_2 &lt; 0.001 )</td>
</tr>
<tr>
<td>TCI dose (( \mu )g ml(^{-1}))</td>
<td>2.9, sd 0.86</td>
<td>4.0, sd 0.80, ( P_1 &lt; 0.001 )</td>
<td>5.4, sd 1.0, ( P_2 &lt; 0.001 )</td>
</tr>
<tr>
<td>Propofol ( C_b ) (( \mu )g ml(^{-1}))</td>
<td>3.0, sd 0.90</td>
<td>4.5, sd 1.0, ( P_1 &lt; 0.001 )</td>
<td>6.5, sd 1.2, ( P_2 &lt; 0.001 )</td>
</tr>
<tr>
<td>BIS</td>
<td>54, sd 13</td>
<td>39, sd 8, ( P_1 &lt; 0.001 )</td>
<td>29, sd 7, ( P_2 &lt; 0.001 )</td>
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in cardiac function is most probably attributable to a decrease in afterload. This phenomenon is also seen in, for example, septic shock models.25

Clinical implications

Several textbooks describe a propofol-induced decrease in CO after an induction dose.21 22 We show that this does not occur with a wide range of propofol effect site concentrations, as used during the maintenance of anaesthesia or sedation. Rather, propofol appears to produce a dose-dependent decrease in arterial pressure by a decrease in stressed volume without a change in CO. The decrease in stressed volume associated with propofol infusion suggests that hypovolaemic patients will have a more pronounced decrease in arterial blood pressure. It is also likely that fluid loading will have a beneficial effect on propofol-induced hypotension. Patients with congestive heart failure may, however, benefit from the propofol-induced decrease in cardiac preload and afterload, because this will most probably enhance CO and reduce cardiac and pulmonary filling pressures.

Study limitations

Although we performed our study in only 17 subjects, the responses were specific and uniform and reached statistical significance. The propofol C9 that we used in our study protocol (3.0–6.5 µg ml−1) are commonly used during anaesthetic maintenance, as shown by the adequate depth of anaesthesia measured with BIS. After an induction or bolus dose, however, peak plasma propofol concentrations are much higher and may even reach 80–100 µg ml−1.21 Most research on the haemodynamic effects of propofol has been performed with bolus administration of propofol, which might be a reason for the differences seen in cardiac function compared with our study. Also, co-administration of opioids with propofol infusion could further affect filling pressures and CO.

The propofol C9 used was not the same in each subject included in our study. Given that the aim was to investigate the haemodynamic changes after a change in propofol C9, we had to choose three separate targets of propofol concentration that were haemodynamically feasible and produced adequate anaesthetic depth in the individual subjects without making alterations in other (i.e. vasoactive) drugs. Nevertheless, propofol C9 and, more importantly, haemodynamic responses proved to be fairly uniform.

The method of measuring MSFP using the inspiratory hold method has never been validated in humans by comparing it with MSFP by total circulatory stop flow.23 However, measuring MSFP with ventilatory manoeuvres is comparable to MSFP measurements using circulatory stop flow in intact dogs.24 We think the method used in the present study is a useful and minimally invasive way to investigate haemodynamic pharmacodynamics in patients.

Conclusions

Increases in propofol C9 within the therapeutic range decrease vascular stressed volume without a change in CO. The absence of an effect of propofol on CO can be explained by the balance between the decrease in effective, or stressed, volume (as determined by MSFP), the decrease in resistance for venous return, and slightly improved heart function.

Authors’ contributions

Study conception: J.R.J., B.F.G.
Data collection: F.deW., A.L.vanV., R.B.deW., J.V., B.F.G.
Drafting the manuscript: F.deW., A.L.vanV., R.B.deW., J.V., J.R.J., J.V., L.P.A., E.deJ., D.P.V., B.F.G.
All authors read and approved the final manuscript.

Declaration of interest

B.F.G. and D.P.V. have performed consultancy work on behalf of their hospital employer for Edwards Lifesciences LLC. The other authors have no conflicts to declare.

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