Plasma propofol concentration and EEG burst suppression ratio during normothermic cardiopulmonary bypass

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Background. During cardiopulmonary bypass (CPB), several factors affect drug disposition and action. This topic has not been studied extensively during normothermic CPB. In this study, we related propofol dose to plasma propofol concentration and burst suppression of the EEG during normothermic bypass.

Methods. After institutional approval and informed consent, 45 patients having cardiac surgery were assigned randomly to receive propofol infusions at 4 (Group A), 5 (Group B) and 6 (Group C) mg kg⁻¹ h⁻¹ during normothermic CPB. In all patients, small to moderate doses of fentanyl were also administered. Plasma propofol concentration and burst suppression ratio (BSR) were measured at the following times: (1) 10 min before CPB, (2) 10 min after the start of CPB, (3) 30 min after the start of the CPB, (4) just after aortic declamping, and (5) 60 min after CPB.

Results. At baseline, plasma propofol concentrations were similar among the three groups. After the start of CPB, the concentrations of propofol decreased significantly by 41, 35, and 30% of control values in Groups A, B, and C, respectively. In Group A, the concentration of propofol during CPB remained unchanged at less than the concentration before bypass. In Groups B and C, plasma propofol concentrations gradually increased during CPB to the pre-bypass concentrations. In Group A, BSR values did not change significantly during CPB. In Groups B and C, BSR values gradually increased and became significantly greater than baseline values. No patient reported intraoperative awareness.

Conclusion. The pharmacokinetics and pharmacodynamics of propofol change during normothermic CPB. During normothermic CPB, the efficacy of propofol may be enhanced compared with before CPB.

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Propofol has been used as a hypnotic agent during cardiopulmonary bypass (CPB), but the pharmacokinetics and pharmacodynamics of propofol during CPB are not well known. During CPB, factors such as haemodilution at the start of CPB, reduced clearance caused by changes in renal and hepatic blood flow, changes in free compared with bound drug, absorption of drugs by CPB apparatus, and hypothermia,¹⁻⁴ could affect drug disposition, metabolism, and elimination.

For the past 25 yr, hypothermia has been used predominantly during CPB for cardiac surgery. Hammaren and colleagues⁵ studied plasma propofol concentration and the latency of the Nb wave of the auditory evoked potential, as a possible indicator of anaesthetic depth, during hypothermic CPB. They found that CPB decreased mean propofol concentration from 2.6 to 1.7 µg ml⁻¹ during a propofol infusion at a rate of 3 mg kg⁻¹ h⁻¹, and the latency of the Nb wave was prolonged compared with baseline values measured before CPB. Dawson and colleagues⁶ found concentrations of propofol ranging from 0.64 (SD 0.07)
to 0.91 (0.11) μg ml⁻¹ during a propofol infusion of
3 mg kg⁻¹ h⁻¹ during hypothermic CPB. Schmidlin and
colleagues⁷ measured the bispectral index (BIS), an index
derived from the EEG that can indicate anaesthetic effect,
during hypothermic CPB. With a mean propofol infusion
rate of 2.0 mg kg⁻¹ h⁻¹ (range from 1.6 to 2.4 mg kg⁻¹ h⁻¹),
the median BIS score was 41 (95% confidence interval
39–42), suggesting that this dose was sufficient. In these
studies, intraoperative awareness was not documented.
Although plasma concentrations of propofol from 2 to
4 μg ml⁻¹ are considered to be effective when propofol
is combined with opioids,⁸ the data above suggest that
smaller concentrations of propofol could provide sufficient
anaesthesia in patients undergoing hypothermic CPB.

Many centres now use normothermic CPB because
bypass and operating time are less, and myocardial protec-
tion and coagulation function are better preserved.
However, normothermic CPB could allow awareness during
surgery more easily. Schmidlin and colleagues⁷ found that
with similar propofol doses, BIS scores were greater during
normothermic CPB than hypothermic CPB, suggesting that
more propofol is required for normothermic patients. In
addition, the effects of CPB on pharmacokinetics may differ
between hypothermia and normothermia, but we know little
about the pharmacokinetics and pharmacodynamics of
propofol during normothermic CPB. We therefore studied
the plasma propofol concentration while propofol was given
at rates of 4, 5, and 6 mg kg⁻¹ h⁻¹ during normothermic
CPB. We also assessed a processed EEG to measure burst
suppression ratio (BSR) as an index of cerebral cortical
activity.

Methods
After institutional approval, informed consent was obtained
from 45 patients (11 women and 34 men, aged 37–85 yr)
undergoing cardiac surgery. Patients with a history of
cerebrovascular disease were excluded. Patients were
randomly assigned to receive propofol at 4 (Group A), 5
(Group B), or 6 mg kg⁻¹ h⁻¹ i.v. (Group C) using the sealed
envelope technique in block randomization with 15 in each
group. The sealed envelope that contained the group
allocation was opened before starting of CPB.

Morphine 0.15 mg kg⁻¹ i.m. and atropine 0.01 mg kg⁻¹
i.m. were given for pre-medication. Anaesthesia was
induced with fentanyl 10 μg kg⁻¹ and propofol. Propofol
administration was controlled with a computer-controlled
syringe pump (Graseby 3400). The computer ran a program
(Stelpump) written by Coetzee JF, MD (University of
Stellenbosch, Department of Anaesthesiology, PO Box
19063, 7505 Tygergerg, South Africa) available from the
website (http://www.sed.sun.ac.za). Stelpump adjusts the
infusion rate to obtain a constant predicted concentration at
the effect site. We used the model of Marsh⁹ in Stelpump.
Coetzee and colleagues¹⁰ found that this model gave
appropriate propofol target prediction within the range
3–6 μg ml⁻¹. For induction, the target effect-site concen-
tration of propofol was set at 3 μg ml⁻¹. A 20- or 22-G
Teflon cannula (2.5 cm in length, Baxter, Deerfield, IL,
USA) was placed in the right radial artery to monitor arterial
pressure and tracheal intubation was facilitated with
vecuronium 0.2 mg kg⁻¹. Anaesthesia was maintained
with an infusion of fentanyl 5 μg kg⁻¹ h⁻¹ (to a total of
30 μg kg⁻¹) and the target controlled propofol infusion.
When CPB started, propofol was given according to the
random allocation. The lungs were mechanically ventilated
with oxygen 50% and nitrous oxide 50% to maintain a P_{aCO₂}
of between 35 and 45 mm Hg.

After induction of anaesthesia, a Swan–Ganz catheter
(Baxter Healthcare Corp., Model 93A-741H-7.5F) was
inserted through the right jugular vein and advanced until
the tip lay in the pulmonary artery. The tympanic membrane
temperature was also monitored continuously (Mon-a
Therm, Mallinckrodt Co., St Louis, MO, USA).

The bypass machine was primed with crystalloid (Lactate
Ringer’s solution containing NaHCO₃, mannitol, tranexa-
mic acid, flomoxef, and prednisolone: 2000 ml) and a non-
pulsatile pump flow rate of 2.8–3.2 litre min⁻¹ m⁻² was set.
Extracorporeal filtration was used to maintain haematocrit
values >20%. After cross-clamping, cardioplegia was
administered. Blood cardioplegia consisting of a mixture
of four parts autologous blood to one part potassium-
enriched cardioplegia solution (40 meq KCl and 30 units of
insulin per litre crystalloid) was delivered every 20–30 min.
A membrane oxygenator and a 40-μm arterial cannula filter
were used. P_{aCO₂}, uncorrected for temperature, was adjusted
to normocapnic levels (35–40 mm Hg) by varying fresh gas
flow to the membrane oxygenator (alpha-stat regulation).
The target rectal temperature was 36°C. Phenylephrine
infusion was used during CPB to maintain mean arterial
pressure (MAP) of 50–70 mm Hg.

A Dräger monitor (Dräger AG, Lübeck, Germany) was
used to monitor the continuously processed EEG. Disposable
electrodes were placed over each frontal and mastoid area on both sides and a reference electrode was placed in the frontal midline. Electrodes were placed using EEG paste (Elefix, Nihon Koden Corp., Tokyo, Japan) and the impedance of the electrodes was checked every 3 min and maintained below 5 kΩ during the study. The EEG was monitored continuously from induction of anaesthesia to emergence. EEG data were recorded onto a PC-compatible computer to display the trend of BSR and raw EEG waveform. After surgery the raw EEG was inspected to ensure that artifacts caused by diathermy were excluded in the off-line analysis. Burst suppression was measured as the BSR. To calculate BSR, suppression is recognized as those periods longer than 0.5 s during which EEG voltage amplitude is less than 5 mV. Time in a suppressed state is measured and BSR is reported as the fraction of the epoch where the EEG is suppressed. Because of the variable (non-
stationary) nature of burst suppression, BSR is averaged

123
over at least 15 epochs (60 s).\textsuperscript{11} Data for BSR were averaged over 10 consecutive artifact-free epochs.

For the measurement of propofol concentration, 5 ml samples were collected from the radial artery catheter. Each blood sample was immediately centrifuged (3000 rpm, 5 min) and serum was stored at ±30°C until analysis. For extraction, 0.2 ml serum was placed in a polypropylene test tube and 1 ml ethyl acetate and 0.1 ml NaOH (50 mM) were added. The tube was shaken for 5 min. The mixture was centrifuged at 15 000 rpm for 5 min, and a 0.9 ml aliquot of the upper ethyl acetate phase was removed and freeze-dried. The freeze-dried pellet was re-dissolved by 0.05 ml mobile phase and injected into a high-pressure liquid chromatograph system: pump (655A-11; Hitachi, Japan), UV absorbance detector (Waters 486; Waters Associates, Milford, MA, USA), and phenyl reverse-phase column (Micro Bondasphere 5-micro phenyl 100A; Waters Associates, Milford, MA, USA). The mobile phase was methanol-100 mM phosphate buffer (pH 2.8) (6:4, v/v), and the flow-rate was 0.8 ml h\textsuperscript{-1}. The wavelength of UV detection was 270 nm. With this method, the standard curve for propofol concentrations in the plasma was linear between 0.2 and 15 μg ml\textsuperscript{-1}. Concentrations of serum total protein were measured with the Biuret method.

Propofol concentration, haemodynamic values, cerebral oxygenation data, and BSR were measured at the following times; (1) 10 min before the start of CPB (time 1), (2) 10 min after the start of CPB (time 2), (3) at 30 min after the start of CPB (time 3), (4) just after de-clamping of the aorta (time 4), and (5) 60 min after CPB (time 5).

Data were expressed as mean (SD). Statistical comparisons used two-way ANOVA for repeated measurement and \(\chi^2\)-test. Fisher’s PLSD test was used for post hoc pair-wise comparisons. \(P<0.05\) was considered significant.

### Results

Patient details are shown in Table 1. Physiological data are shown in Table 2. There were no significant differences in MAP, body temperature, haemoglobin, and \(P_{aCO_2}\) among the three groups. Significant changes in MAP, body temperature, haemoglobin, pH, \(P_{aO_2}\) and \(P_{aCO_2}\) occurred during CPB.

Figure 1 shows the changes in propofol concentration, BSR and concentrations of serum total protein during the study period. Before the start of CPB (time 1), there were no significant differences in propofol concentration among the three groups (Group A=2.3 (0.8) μg ml\textsuperscript{-1}, Group B=2.4 (0.7) μg ml\textsuperscript{-1}, and Group C=2.6 (0.7) μg ml\textsuperscript{-1}). Ten minutes after starting CPB (time 2), plasma propofol concentration decreased by 41, 35, and 30% of the baseline values in Groups A, B, and C, respectively. In Group A, the concentration of propofol remained unchanged at less than the pre-bypass level during CPB. In Groups B and C, plasma propofol during CPB concentrations gradually increased to pre-bypass level. Plasma propofol concentrations at time 3

### Table 1 Patient details. Data are mean (range)

<table>
<thead>
<tr>
<th>Patient details</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>68 (49–85)</td>
<td>65 (43–75)</td>
<td>67 (37–79)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>58 (37.5–88)</td>
<td>59 (46–75)</td>
<td>60 (45–85)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>156 (141–165)</td>
<td>162 (151–173)</td>
<td>158 (144–177)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>10/5</td>
<td>13/2</td>
<td>11/4</td>
</tr>
<tr>
<td>Coronary artery bypass</td>
<td>15</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Valve surgery (n)</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>285 (235–400)</td>
<td>321 (210–440)</td>
<td>318 (240–500)</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>100 (72–149)</td>
<td>122 (77–189)</td>
<td>121 (79–164)</td>
</tr>
</tbody>
</table>

### Table 2 Clinical data given as mean (sd). There were no significant differences between Groups A, B, and C. Each variable was measured at the following times; (1) 10 min before the start of CPB, (2) 10 min after the start of CPB, (3) 30 min after the start of CPB, (4) after de-clamping of the aorta, (5) 60 min after CPB. \(P<0.05\) vs time 1

<table>
<thead>
<tr>
<th>Time</th>
<th>Group</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>A (4 mg kg\textsuperscript{-1} h\textsuperscript{-1})</td>
<td>73 (11)</td>
<td>57 (11)</td>
<td>60 (13)</td>
<td>47 (5)</td>
<td>69 (12)</td>
</tr>
<tr>
<td></td>
<td>B (5 mg kg\textsuperscript{-1} h\textsuperscript{-1})</td>
<td>74 (12)</td>
<td>55 (7)</td>
<td>54 (9)</td>
<td>47 (4)</td>
<td>66 (12)</td>
</tr>
<tr>
<td></td>
<td>C (6 mg kg\textsuperscript{-1} h\textsuperscript{-1})</td>
<td>69 (9)</td>
<td>63 (13)</td>
<td>57 (12)</td>
<td>48 (6)</td>
<td>63 (9)</td>
</tr>
<tr>
<td>Body temperature (°C)</td>
<td>A (4 mg kg\textsuperscript{-1} h\textsuperscript{-1})</td>
<td>35.7 (0.4)</td>
<td>36.0 (0.5)</td>
<td>36.6 (0.3)</td>
<td>36.8 (0.3)</td>
<td>36.6 (0.2)</td>
</tr>
<tr>
<td></td>
<td>B (5 mg kg\textsuperscript{-1} h\textsuperscript{-1})</td>
<td>35.7 (0.6)</td>
<td>36.0 (0.5)</td>
<td>36.5 (0.2)</td>
<td>36.6 (0.2)</td>
<td>36.9 (0.2)</td>
</tr>
<tr>
<td></td>
<td>C (6 mg kg\textsuperscript{-1} h\textsuperscript{-1})</td>
<td>35.9 (0.9)</td>
<td>36.0 (0.8)</td>
<td>36.4 (0.6)</td>
<td>36.5 (0.4)</td>
<td>36.4 (0.6)</td>
</tr>
<tr>
<td>Haemoglobin (g dl\textsuperscript{-1})</td>
<td>A (4 mg kg\textsuperscript{-1} h\textsuperscript{-1})</td>
<td>10.4 (1.6)</td>
<td>6.2 (1.3)</td>
<td>6.5 (0.9)</td>
<td>6.6 (1.2)</td>
<td>8.4 (1.6)</td>
</tr>
<tr>
<td></td>
<td>B (5 mg kg\textsuperscript{-1} h\textsuperscript{-1})</td>
<td>11.8 (1.6)</td>
<td>6.9 (0.9)</td>
<td>7.1 (1.0)</td>
<td>6.8 (0.9)</td>
<td>8.4 (1.1)</td>
</tr>
<tr>
<td></td>
<td>C (6 mg kg\textsuperscript{-1} h\textsuperscript{-1})</td>
<td>10.9 (1.4)</td>
<td>6.6 (1.0)</td>
<td>6.7 (0.9)</td>
<td>7.1 (0.8)</td>
<td>8.8 (1.1)</td>
</tr>
<tr>
<td>pH</td>
<td>A (4 mg kg\textsuperscript{-1} h\textsuperscript{-1})</td>
<td>7.43 (0.02)</td>
<td>7.41 (0.04)</td>
<td>7.41 (0.02)</td>
<td>7.40 (0.02)</td>
<td>7.40 (0.03)</td>
</tr>
<tr>
<td></td>
<td>B (5 mg kg\textsuperscript{-1} h\textsuperscript{-1})</td>
<td>7.43 (0.03)</td>
<td>7.44 (0.03)</td>
<td>7.42 (0.03)</td>
<td>7.42 (0.03)</td>
<td>7.36 (0.003)</td>
</tr>
<tr>
<td></td>
<td>C (6 mg kg\textsuperscript{-1} h\textsuperscript{-1})</td>
<td>7.42 (0.04)</td>
<td>7.41 (0.03)</td>
<td>7.39 (0.05)</td>
<td>7.39 (0.05)</td>
<td>7.38 (0.05)</td>
</tr>
<tr>
<td>(P_{aO_2}) (mm Hg)</td>
<td>A (4 mg kg\textsuperscript{-1} h\textsuperscript{-1})</td>
<td>186 (58)</td>
<td>391 (85)</td>
<td>371 (87)</td>
<td>383 (108)</td>
<td>250 (93)</td>
</tr>
<tr>
<td></td>
<td>B (5 mg kg\textsuperscript{-1} h\textsuperscript{-1})</td>
<td>205 (40)</td>
<td>392 (73)</td>
<td>351 (60)</td>
<td>344 (64)</td>
<td>230 (110)</td>
</tr>
<tr>
<td></td>
<td>C (6 mg kg\textsuperscript{-1} h\textsuperscript{-1})</td>
<td>187 (64)</td>
<td>407 (74)</td>
<td>399 (111)</td>
<td>428 (96)</td>
<td>246 (136)</td>
</tr>
<tr>
<td>(P_{aCO_2}) (mm Hg)</td>
<td>A (4 mg kg\textsuperscript{-1} h\textsuperscript{-1})</td>
<td>37 (3)</td>
<td>41 (3)</td>
<td>41 (2)</td>
<td>41 (2)</td>
<td>41 (3)</td>
</tr>
<tr>
<td></td>
<td>B (5 mg kg\textsuperscript{-1} h\textsuperscript{-1})</td>
<td>40 (4)</td>
<td>39 (2)</td>
<td>39 (2)</td>
<td>40 (2)</td>
<td>42 (4)</td>
</tr>
<tr>
<td></td>
<td>C (6 mg kg\textsuperscript{-1} h\textsuperscript{-1})</td>
<td>38 (4)</td>
<td>41 (2)</td>
<td>40 (3)</td>
<td>40 (2)</td>
<td>41 (2)</td>
</tr>
</tbody>
</table>
in Group C and at times 4 and 5 in Groups B and C were significantly greater than those in Group A (*P<0.05).

At baseline (time 1), BSR values were similar among the three groups. In Group A, BSR values did not change significantly during CPB. In Groups B and C, BSR values gradually increased and became significantly greater than the baseline values. Values of BSR at time 3 in Group C and at times 4 and 5 in Groups B and C were significantly greater than those in Group A (**P<0.05). There were no significant differences in concentrations of serum total protein among the three groups. The values of total protein at time 2 were significantly less than the control values in all groups. No patient reported awareness of intraoperative events.

**Discussion**

We found that CPB reduced plasma propofol concentration. In patients receiving propofol infusion at 4 mg kg⁻¹ h⁻¹, propofol concentration and BSR remained unchanged at less than or close to the pre-bypass level, respectively, during normothermic CPB. In contrast, in patients receiving propofol of 5 or 6 mg kg⁻¹ h⁻¹, propofol concentration and BSR values gradually increased to greater than above the pre-bypass value during normothermic CPB.

Starting hypothermic CPB can reduce propofol concentration probably by haemodilution. Russell and colleagues reported that propofol concentration decreased to 50–78% of pre-bypass level at 2–10 min after starting hypothermic CPB. Dawson and colleagues reported that propofol concentration decreased to 60% at the start of hypothermic CPB. The present study supports these studies. Propofol concentrations decreased to 59–70% of pre-bypass level after the onset of normothermic CPB. Since body temperature decreases for a short period after the induction of hypothermic CPB, the decrease in propofol concentrations after starting CPB may be dilution by the pump prime in both the normothermic and hypothermic patients.

However, in previous studies of propofol concentrations during hypothermic CPB, the concentration of propofol increased to the pre-bypass level promptly after the induction of CPB. Dawson and colleagues found that with propofol administration at 3 mg kg⁻¹ h⁻¹ the decrease in propofol concentration was maximal within the first 3 min of the onset of CPB and returned to pre-bypass level after 20 min. In our study, at an infusion rate of 4 mg kg⁻¹ h⁻¹ using propofol concentration did not return to the pre-bypass level. The reasons for this difference are unknown. Since the metabolic rate increases exponentially with body temperature, elimination might be greater during normothermic CPB than hypothermic CPB. McMurray and colleagues found that the clearance of propofol was reduced and the half-life was prolonged in cardiac surgery with hypothermic CPB.

It has been suggested that, during opioid supplementation, plasma concentrations of propofol should be >2–4 µg ml⁻¹ to avoid intraoperative awareness. However, in the present study, the mean propofol concentration was less than these values and ranged from 1.3 to 1.5 µg ml⁻¹ in Group A during infusion at 4 mg kg⁻¹ h⁻¹. In these patients, intraoperative awareness was not reported. Furthermore, burst suppression develops during CPB in Groups B and C, although the plasma concentration of propofol during CPB (time 4) is similar to baseline values. In Groups B and C the mean propofol concentrations, at which burst suppression developed, ranged from 2.1 to 2.2 µg ml⁻¹. Burst suppres-
sion usually needs higher concentrations of propofol without CPB. Doyle and colleagues reported that a mean infusion rate of 13.6 mg kg\(^{-1}\) h\(^{-1}\) (range 8.5–28.6 mg kg\(^{-1}\) h\(^{-1}\)) of propofol was needed to suppress the EEG. Although the patient population was different, Van Hemelrijck and colleagues found that blood propofol concentrations of 6.3 (1.4) \(\mu\)g ml\(^{-1}\) were needed to cause burst suppression during normoanaesthesia. These results suggest that the efficacy of propofol during normothermic CPB may be enhanced compared with normothermia without CPB.

The action of propofol may be enhanced for the following reasons. Propofol exists in plasma in two forms: unbound and bound to protein. The unbound propofol is pharmacologically active. Kumar and colleagues postulated that haemodilution could affect the unbound fraction of drug. Hammaren and colleagues studied the changes in total and unbound propofol concentrations and the latency of Nb wave of auditory evoked potentials during hypothermic CPB. They found that although total propofol concentration decreased, unbound propofol concentration did not decrease and Nb wave latency was prolonged. This suggested that changes in total and unbound concentrations of propofol were not parallel during hypothermic CPB. Dawson and colleagues also reported that the onset of hypothermic CPB caused a decrease in total propofol concentrations, but the unbound concentrations remained stable. Although we did not measure the unbound propofol concentrations in the present study, our data suggest that the free propofol concentrations could remain unchanged or increase during normothermic CPB. This speculation requires further study.

Can the degree of sedation be assessed by BSR? Originally we planned to use spectral edge frequency 90 to assess sedation. However, the presence of burst suppression during normothermic CPB affected the interpretation of this index. Therefore, we used the BSR. In Groups B and C, as the BSR increased during normothermic CPB at least, the level of sedation seems to be more than pre-bypass. Although there was no intraoperative awaking, it is not clear if the sedation level is appropriate in Group A from the BSR values alone. Hirschi and colleagues demonstrated that bispectral EEG remained unchanged with a continuous infusion of propofol [4.4 (1.8) mg kg\(^{-1}\) h\(^{-1}\), mean (SD)] during normothermic CPB compared with pre-bypass level. These are compatible with the present study. However, further studies are needed using other methods such as bispectral EEG analysis and mid-latency auditory evoked potentials, for the assessment of sedation level.

In summary, we investigated plasma propofol concentrations and burst suppression during normothermic CPB. The results suggest that the pharmacokinetics and pharmacodynamics of propofol could change under normothermic CPB. With propofol infusion at a rate of 5 and 6 mg kg\(^{-1}\) h\(^{-1}\), anaesthesia can be achieved with mild to moderate doses of fentanyl. The efficacy of propofol appears to be enhanced during normothermic CPB. When propofol is given at 4 mg kg\(^{-1}\) h\(^{-1}\), monitoring of sedation level is recommended.

References

126