EFFECT OF THIOPENTONE, ETOMIDATE AND PROPOFOL ON SYSTEMIC VASCULAR RESISTANCE DURING CARDIOPULMONARY BYPASS

F. BOER, J. G. BOVILL, P. ROS AND H. VAN OMMEN

SUMMARY
We have studied the effect of thiopentone, etomidate and propofol on systemic vascular resistance (SVR) during cardiopulmonary bypass with constant pump flow in 30 patients undergoing elective coronary artery bypass surgery. SVR decreased to 78% of control values after thiopentone 4 mg kg$^{-1}$, to 72% of control after etomidate 0.3 mg kg$^{-1}$, and to 68% of control after propofol 2 mg kg$^{-1}$; it returned to control values 10 min after administration of thiopentone and propofol and 7 min after administration of etomidate. Analysis of variance showed that there were no significant differences in the changes in SVR between the groups.

KEY WORDS
Anaesthetic, intravenous: propofol, thiopentone, etomidate. Heart, vascular pressures.

Most of the i.v. anaesthetic drugs cause, to a lesser or greater degree, cardiovascular depression. The observed cardiovascular effects of a drug are the result of complex interactions between changes in systemic vascular resistance (SVR), heart rate, baroreflex activity and myocardial contractility. Cardiopulmonary bypass (CPB) has been used to study the isolated effects of drugs on the peripheral circulation [1–3]. In a previous study we used this model to study the effect of propofol on SVR [4]. In the present study we have compared the effect of propofol, thiopentone and etomidate, in doses used for induction of anaesthesia, on SVR during CPB.

PATIENTS AND METHODS
We studied 30 patients undergoing elective aortocoronary bypass grafting (CABG) surgery. The study was approved by the local Ethics Committee and all patients gave informed consent. All patients were receiving β-adrenoceptor antagonists, calcium antagonists and nitrates which were continued until surgery. Lorazepam 2–4 mg sublingually was given 90 min before the patient arrived in the operating theatre, where an i.v. infusion was commenced and a radial artery catheter inserted under local anaesthesia. The radial artery catheter was connected to a disposable pressure transducer (Gobuplast, Hillegom, The Netherlands) which was calibrated electronically before surgery.

Anaesthesia was induced with sufentanil 4–8 µg kg$^{-1}$. Pancuronium 100 µg kg$^{-1}$ was given to provide neuromuscular block and, after intubation of the trachea, the patient’s lungs were ventilated with an oxygen–air mixture ($F_{O_2}$ 0.5). Anaesthesia was maintained with sufentanil 0.05–0.1 µg kg$^{-1}$ min$^{-1}$. During CPB the infusion of sufentanil was reduced to 0.025 µg kg$^{-1}$ min$^{-1}$. CPB was conducted with a membrane oxygenator using non-pulsatile flow with a pump flow index of 1.6–1.8 litre min$^{-1}$ m$^{-2}$ and moderate hypothermia (26–28 °C). The extracorporeal bypass circuit was primed with Ringer’s solution 1400 ml, human albumin 200 ml and 20 % mannitol 100 ml.

Any patient who had been given a vasoactive drug before or during CPB was excluded from the study. When nasopharyngeal temperature and pump flow had been stable for 5 min, patients were allocated randomly (coded envelope) to receive thiopentone 4 mg kg$^{-1}$, etomidate 0.3 mg kg$^{-1}$ or propofol 2 mg kg$^{-1}$. Perfusion pressure, pump flow and temperature were measured every 30 s for a further 5 min. The mean value of SVR

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calculated during the last 2.5 min was taken as the control value. The test drug was injected into the venous inflow of the oxygenator and recordings continued for at least 10 min or until cardioplegic solution was given, the pump flow was changed or the aortic clamp was released.

In all patients, systemic arterial pressure measured via the radial artery was taken to indicate perfusion pressure during cardiopulmonary bypass. SVR was calculated as:

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\text{SVR} = \frac{\text{perfusion pressure (mm Hg)}}{\text{pump flow (litre min}^{-1})} \times 80 \text{ dyn s cm}^{-2}
\]

Patient data were compared by one-factor analysis of variance. SVR values were compared using three-factor block design analysis of variance, with group, individual and time as the factors (NCSS program, Hinze JL, Kaysville, Utah, U.S.A.). Differences within groups were compared using Fisher's LSD test. \(P < 0.05\) was taken as statistically significant. Results are presented as mean (SD).

**RESULTS**

There were no statistically significant differences in patient data, pre-drug pump flow, perfusion pressure, \(P_{aO_2}\) or PCV between the three groups of patients (table I). Complete recordings were obtained for 10 min for all patients in the propofol group and for eight patients in the thiopentone and etomidate groups.

SVR was significantly decreased compared with control by 1 min after drug administration in the etomidate and propofol groups and by 1.5 min in the thiopentone group (table II). It remained significantly less than control for 10 min in the thiopentone and propofol groups, and for 6 min in the etomidate group. Analysis of variance demonstrated no statistical difference between groups with respect to the time course of changes in SVR (\(P = 0.75\), df = 266 and 18, \(P = 0.7574\)).

**DISCUSSION**

We have shown that thiopentone, etomidate and propofol, given during CPB in doses comparable to those used for induction of anaesthesia, caused similar and significant decreases in SVR. These findings are similar to those reported previously for propofol [4] and for thiopentone [5]. In contrast, Pauca and Roy [6] found that thiopentone 250 mg given during CPB resulted in only a temporary decrease in perfusion pressure, lasting 40 s. These investigators used a faster pump flow (2.0–2.8 litre min\(^{-1}\) m\(^{-2}\)) than we did, and this may have contributed to the shortlived hypotensive effect of thiopentone in their study.

The haemodynamic effects of propofol and etomidate have been studied in patients who had a Jarvik-7 artificial heart implant whilst waiting for cardiac transplantation [7]. The artificial heart was set to provide a constant cardiac output independent of changes in preload. This system is similar to our CPB model in that it allows the systemic vascular effects of a drug to be studied independent of changes in cardiac output or heart rate. In these patients, propofol 2.5 mg kg\(^{-1}\) reduced mean arterial pressure, and therefore SVR, by 61% [7]. Arterial pressure remained significantly less than the pre-drug value for 30 min. In contrast to propofol, etomidate 0.3 mg kg\(^{-1}\) did not change any haemodynamic variables [8]. This is in contrast with our study in which etomidate caused a decrease in SVR similar to that produced by propofol. A possible ex-
propofol resulted in a significant decrease [11]. Other studies have described [12], others found no decrease [13–15].

These differences may reflect differences in patient populations, combinations with other drugs and possibly the ventilatory status of the patient.

The differences in the systemic vascular effects of thiopentone, etomidate and propofol in our study and in those in which they were used to induce anaesthesia may be related to the circumstances pertaining during CPB. In particular, the use of non-pulsatile flow and hypothermia may have altered the sensitivity of vascular smooth muscle to the vasodilating effects of these drugs. The decrease in SVR produced by droperidol is of longer duration during non-pulsatile flow compared with pulsatile flow [3]. All three drugs are moderately to highly bound to plasma proteins: thiopentone 80–84 % [16, 17], etomidate 70–75 % [18, 19], propofol 98 % [20]. Thus haemodilution during CPB results in an increase in the free fraction of unbound drug, with a corresponding increase in pharmacological effect. The free fraction of propofol increases 1.5–3 fold during bypass [21]. The use of heparin during CPB, by increasing non-esterified fatty acids, may further decrease the binding of drug to plasma proteins [22]. All our patients were taking β-adrenoceptor antagonists and calcium entry blockers. These drugs may have influenced the results. It is also possible that the large concentrations of sufentanil used during the study have altered systemic vascular sensitivity to the

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**TABLE II. Changes in systemic vascular resistance (SVR) after thiopentone, etomidate or propofol (mean (sd)). *P < 0.05. N = No. patients**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Thiopentone 4 mg kg⁻¹</th>
<th>Etomidate 0.3 mg kg⁻¹</th>
<th>Propofol 2 mg kg⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SVR (dyn s cm⁻⁴)</td>
<td>SVR (dyn s cm⁻⁴)</td>
<td>SVR (dyn s cm⁻⁴)</td>
</tr>
<tr>
<td>Control</td>
<td>10 1768 (315)</td>
<td>10 1639 (183)</td>
<td>10 1528 (199)</td>
</tr>
<tr>
<td>0.5</td>
<td>10 1829 (357)</td>
<td>10 1733 (217)</td>
<td>10 1574 (205)</td>
</tr>
<tr>
<td>1</td>
<td>10 1790 (352)</td>
<td>10 1327 (256)*</td>
<td>10 1260 (323)*</td>
</tr>
<tr>
<td>1.5</td>
<td>10 1405 (310)*</td>
<td>10 1176 (282)*</td>
<td>10 1042 (271)*</td>
</tr>
<tr>
<td>2</td>
<td>10 1382 (393)*</td>
<td>10 1239 (289)*</td>
<td>10 1063 (246)*</td>
</tr>
<tr>
<td>2.5</td>
<td>10 1489 (446)*</td>
<td>10 1278 (296)*</td>
<td>10 1120 (260)*</td>
</tr>
<tr>
<td>3</td>
<td>10 1558 (459)*</td>
<td>10 1330 (258)*</td>
<td>10 1153 (260)*</td>
</tr>
<tr>
<td>3.5</td>
<td>10 1593 (489)*</td>
<td>10 1381 (292)*</td>
<td>10 1184 (246)*</td>
</tr>
<tr>
<td>4</td>
<td>10 1608 (480)*</td>
<td>10 1387 (248)*</td>
<td>10 1196 (243)*</td>
</tr>
<tr>
<td>4.5</td>
<td>10 1520 (389)*</td>
<td>8 1410 (264)*</td>
<td>10 1217 (247)*</td>
</tr>
<tr>
<td>5</td>
<td>10 1529 (396)*</td>
<td>8 1429 (257)*</td>
<td>10 1229 (244)*</td>
</tr>
<tr>
<td>6</td>
<td>9 1603 (362)*</td>
<td>8 1445 (265)*</td>
<td>10 1235 (250)*</td>
</tr>
<tr>
<td>7</td>
<td>8 1520 (368)*</td>
<td>8 1495 (280)*</td>
<td>10 1253 (274)*</td>
</tr>
<tr>
<td>8</td>
<td>8 1640 (381)*</td>
<td>8 1537 (284)</td>
<td>10 1247 (265)*</td>
</tr>
<tr>
<td>9</td>
<td>8 1612 (311)*</td>
<td>8 1556 (279)</td>
<td>10 1243 (277)*</td>
</tr>
<tr>
<td>10</td>
<td>8 1647 (378)*</td>
<td>8 1554 (273)</td>
<td>10 1282 (237)*</td>
</tr>
</tbody>
</table>
drugs studied. Sufentanil 6 µg kg⁻¹ causes significant vasodilatation in the isolated denervated hindlimb of the dog, an effect that is independent of opioid receptors [23]. Similar vasodilatation is produced by equivalent doses of fentanyl and alfentanil.

ACKNOWLEDGEMENT
The authors are grateful to ICI-Farma, Rotterdam, The Netherlands for financial support.

REFERENCES