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 aorto-coronary 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 (\(F_{\text{IO}}\) 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
TABLE I. Patient characteristics and pre-drug conditions for the three groups (mean (range or SD)).

<table>
<thead>
<tr>
<th></th>
<th>Thiopentone</th>
<th>Etomidate</th>
<th>Propofol</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>59.8 (48-72)</td>
<td>66.0 (46-82)</td>
<td>60.8 (31-75)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.6 (7.9)</td>
<td>80.5 (7.3)</td>
<td>80.0 (10.4)</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.85 (0.13)</td>
<td>1.94 (0.14)</td>
<td>2.00 (0.14)</td>
</tr>
<tr>
<td>Perfusion pressure (mm Hg)</td>
<td>65.7 (11.5)</td>
<td>66.2 (9.3)</td>
<td>64.0 (4.8)</td>
</tr>
<tr>
<td>Flow (litre min⁻¹)</td>
<td>3.48 (0.62)</td>
<td>3.67 (0.60)</td>
<td>3.80 (0.68)</td>
</tr>
<tr>
<td>Pao₂ (kPa)</td>
<td>20.0 (6.4)</td>
<td>19.9 (9.7)</td>
<td>20.9 (3.8)</td>
</tr>
<tr>
<td>PCV</td>
<td>0.23 (0.04)</td>
<td>0.27 (0.04)</td>
<td>0.26 (0.03)</td>
</tr>
</tbody>
</table>

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 indi-
cate perfusion pressure during cardiopulmonary
bypass. SVR was calculated as:

\[ \text{SVR} = \frac{\text{perfusion pressure (mm Hg)}}{\text{pump flow (litre min}^{-1})} \times 80 \text{ dyn s cm}^{-5} \]

Patient data were compared by one-factor
analysis of variance. SVR values were compared
using three-factor block design analysis of vari-
ance, 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 pre-
sented as mean (SD).

RESULTS

There were no statistically significant differences
in patient data, pre-drug pump flow, perfusion
pressure, \( Pao₂ \) 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 demon-
strated no statistical difference between groups
with respect to the time course of changes in SVR
(\( F = 0.75, \text{df} = 266 \text{ and } 18, P = 0.7574 \)).

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, Pauc and Roy [6] found that thio-
pentone 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-
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>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 (246)*</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 1628 (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>

Explanation for the decrease in SVR after etomidate and the other drugs in our patients could be an increase in the depth of anaesthesia from a previously inadequate level. We feel this is unlikely. No patient showed evidence of inadequate anaesthesia before the start of CPB. Although in this study we did not measure plasma catecholamine concentrations, in a previous study [4] in which an identical anaesthetic technique was used, plasma concentrations of adrenaline and noradrenaline were not increased 5–10 min after the start of cardiopulmonary bypass and did not change after administration of propofol. This suggests that anaesthesia with the doses of sufentanil used was adequate. A single bolus of sufentanil 1.3 μg kg⁻¹ produced unconsciousness and a depth of anaesthesia adequate for laryngoscopy [9]. This dose is considerably less than that used in the present study.

Williams and colleagues [10] compared the cardiovascular effects of thiopentone 4 mg kg⁻¹, etomidate 0.3 mg kg⁻¹ and propofol 2.5 mg kg⁻¹ for induction of anaesthesia in patients with coronary artery disease. There were no significant changes in SVR after any of these drugs. Etomidate did not alter SVR in elderly patients undergoing upper abdominal surgery, whereas propofol resulted in a significant decrease [11]. The reported effects of propofol on SVR are conflicting. Whereas a decrease has been 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
drugs studied. Sufentanil 6 \( \mu \text{g \ kg}^{-1} \) 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

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REFERENCES


