EFFECT OF GRADED INFUSION RATES OF PROPOFOL ON REGIONAL AND GLOBAL LEFT VENTRICULAR FUNCTION IN THE DOG†

R. M. PUTTICK, J. DIEDERICKS, J. W. SEAR, J. B. GLEN, P. FOËX AND W. A. RYDER

SUMMARY
We have studied the effects of graded infusion rates of propofol (0.2-0.5 mg kg⁻¹ min⁻¹) on left ventricular global and regional function, in eight acutely instrumented dogs. Global function was assessed by measurement of aortic and left ventricular pressure, LV dP/dt max, aortic blood acceleration and stroke volume. Regional function was assessed by measurement of systolic shortening and the end-systolic pressure-length relationship. The response of the coronary circulation to short periods of occlusion was also assessed. Administration of propofol significantly reduced left ventricular preload, as indicated by reductions in end-diastolic pressure and length; contractility was depressed, the depression being greater in the apex than in the base of the left ventricle. High infusion rates impaired relaxation. Regulation of coronary blood flow was not disrupted. Reductions in preload and contractility contributed to the propofol-induced hypotension. After 60 min, recovery from the greatest infusion rate was incomplete.

KEY WORDS

Propofol has been reported to decrease arterial pressure, systemic vascular resistance, cardiac output and stroke volume [1-4]. The most consistently reported effect of propofol on heart rate is a reduction thought to be caused by a resetting of baroreceptors to allow slower heart rates despite decreases in arterial pressure [5].

The mechanisms thought to account for the hypotension include peripheral vasodilation, reduced ventricular filling and a depression in contractility. Glen and Hunter [6] demonstrated that administration of propofol to mini-pigs produced peripheral vasodilation and, originally, this appeared to be the main determinant of propofol-induced hypotension. More recently, systemic vasodilation was demonstrated when propofol was administered during cardiopulmonary bypass [7]. In contrast with these studies, other investigators have found systemic vascular resistance to be essentially unchanged by propofol [8]. Goodchild and Serrao [9] found an increase in venous capacitance in vagotomized dogs with pharmacologically denervated hearts. This venodilatation is dose-dependent and may contribute to hypotension through reduction of the preload. In the same study, it was shown that large concentrations of propofol caused both peripheral vasodilation and myocardial depression. In addition to changes in venous capacitance and peripheral vascular resistance, a decrease in myocardial contractility may also contribute to the decreased arterial pressure. Indeed, Carlier and colleagues [8] showed that propofol reduced stroke volume with little effect on left ventricular filling pressure, which suggests a depressant effect on myocardial contractility. At a cellular level, propofol has been shown to reduce influx of calcium into guineapig isolated ventricular myocytes [10], thereby decreasing contractility. Another possible factor contributing to the negative inotropic effect is the reduction of catecholamine release by propofol [11].

The aim of this study was to determine the effects of graded doses (infusion rates) of propofol on the cardiovascular system, with particular reference to myocardial function. From the clinicians' point of view, there are few studies describing the dose-concentration-effect relationships for i.v. agents. Sear and Pryz-Roberts [12] proposed the "minimum infusion rate" (MIR) and multiples thereof as one possible index to describe the potency of doses of i.v. agents. However, use of infusion rates as the indicator of dose ignores the kinetic variability that exists for i.v. agents (and hence the differences between predicted and measured drug concen-
trations) [13]. Hence, we have also examined the concentration-effect relationships for propofol in this study.

MATERIALS AND METHODS

This study conformed to the Animals (Scientific Procedure) Act of 1986 (U.K.; Home Office license no PPL 30/00296). Eight dogs of both sexes, mean weight 20.3 kg (range 15.9-22.7 kg) were premedicated with morphine 0.1 mg kg⁻¹ and anaesthetized with thiopentone 15-20 mg kg⁻¹ i.v. The trachea was intubated, the animal placed on the right side, and the lungs ventilated with 70% nitrogen in oxygen at a rate of 12 b.p.m. with a tidal volume of 30 ml kg⁻¹. Oxygen concentration was monitored continuously by paramagnetic analysis. Carbon dioxide was added to the mixture to maintain the end-tidal carbon dioxide concentration at 5.3% as measured continuously by an infra-red carbon dioxide analyser. During the surgical procedure anaesthesia was maintained with 0.7-1.5% halothane using a Fluotec vaporizer (Cyprane, Keighley, U.K.). Mid-oesophageal temperature was monitored and maintained at 36-37 °C using a servo-controlled heating element incorporated into the operating table. An i.v. cannula was inserted via the femoral vein into the inferior vena cava for constant infusion of isotonic sodium chloride (0.154 mol litre⁻¹; 37 °C) at a rate of 5 ml kg⁻¹ h⁻¹. Limb lead II of the ECG was recorded throughout the investigations.

The left common carotid artery was isolated in the neck, and a rigid 8-French gauge (2.76-mm o.d.) cannula, connected to a Druck pressure transducer (Druck Ltd, Groby, Leicester, U.K.), was passed to within 1 cm of the aortic valve to measure systemic arterial pressure and obtain arterial blood samples. A left thoracotomy was performed and the fifth and sixth ribs excised. The pericardium was opened and the proximal arterial pressure and obtain arterial blood samples. A left thoracotomy was performed and the fifth and sixth ribs excised. The pericardium was opened and the proximal aortic root dissected free, and an appropriately sized electromagnetic flow transducer (Transflow 601, Skalar Medical, Delft, Holland), attached to a flowmeter (S.E.M. 275, S.E. Medics, Feltham, U.K.), placed to measure aortic flow. A second rigid 8-French gauge cannula was inserted into the left ventricle, via a stab wound in the apical dimple, and attached to another pressure transducer for measurement of left ventricular pressure. A flexible catheter was inserted into the pulmonary artery via the right ventricular outflow tract for measurement of cardiac output by dye dilution. A segment of the descending thoracic aorta was isolated, and a length of surgical tape placed around the aorta to enable manual aortic constrictions to be made.

A segment of left anterior descending coronary artery (LAD) distal to the first diagonal branch was dissected free from the epicardium for placement of a 2-mm electromagnetic flow transducer. Distal to the flow probe, a snare was placed around the LAD and used for abrupt manual occlusions to obtain zero flow reference points.

Two pairs of piezoelectric crystals (5-MHz, 2-mm diameter) were placed in the subendocardium (in the minor axis of the left ventricle) to measure regional segmental length ultrasonically. One pair was located in an area supplied by the left anterior descending (LAD) coronary artery in the apical region, and the other in an area supplied by the left circumflex (LC) artery in the basal region.

After surgery was completed, anaesthesia with 1% halothane was continued for about 1 h, during which all transducers were calibrated. Halothane was then replaced by propofol which was administered as a bolus dose (5 mg kg⁻¹) over 5 min and after this as a constant infusion at a rate of 0.2 mg kg⁻¹ min⁻¹. A 1-h period was allowed to elapse before recordings were made. A 10-s coronary occlusion and two 6-s aortic occlusions were performed. Blood samples were taken 10 min apart, before and after haemodynamic recordings, for measurement of blood concentrations of propofol. The infusion rate was changed to 0.4 mg kg⁻¹ min⁻¹ for 10 min and then reduced to 0.3 mg kg⁻¹ min⁻¹ for a 25-min equilibration period. After this period, a coronary occlusion and two aortic occlusions were performed. The procedure just described for the 0.3-mg kg⁻¹ min⁻¹ infusion rate was repeated for propofol infusion rates of 0.4 and 0.5 mg kg⁻¹ min⁻¹, infusing at 0.5 and 0.6 mg kg⁻¹ min⁻¹ for the first 10 min, respectively. After the 0.5-mg kg⁻¹ min⁻¹ infusion, the rate was reduced to 0.2 mg kg⁻¹ min⁻¹ in order to test the extent of recovery. After a further 1-h equilibration period, coronary and aortic occlusions were carried out and blood samples were obtained. At the end of the experiment the dog was killed and coronary flow was calibrated by injection of 5-ml aliquots of heparinized blood through the coronary artery with the flow probe in place. The area supplied by the LAD artery was defined by injection of Evans blue dye into the vessel at the site of the flow transducer; careful weighing of the stained muscle allowed mean flow to be calibrated in ml min⁻¹ per 100 g of muscle.

Mean arterial pressure was calculated from systolic and diastolic arterial pressures (SAP and DAP, respectively). The left ventricular pressure signal was fed to an analog differentiator to derive positive and negative LV dP/dt. Systemic vascular resistance (SVR) was calculated as the mean arterial pressure divided by the cardiac output. Coronary perfusion pressure (CPP) was calculated as the difference between the DAP and left ventricular end-diastolic pressure (LVEDP). Coronary vascular resistance was calculated by dividing CPP by coronary blood flow. Peak hyperaemic coronary flow was the greatest value for coronary flow after the 10-s occlusion periods. For normal load conditions, regional data were digitized manually. End-diastolic length (EDL) was measured at the time of the beginning of the sharp upslope of the first derivative of left ventricular pressure (LV dP/dt) signal. End-systolic length (ESL) was measured at the time the aortic flow first returned to zero. The end-systolic pressure-length relationship (ESPLR) was calculated for afterloaded beats. This involved measuring end-systolic pressures and the LAD and LC segment lengths for the first few beats following aortic occlusion. Linear regression analysis was carried out.
TABLE

Effect of increasing infusion rates of propofol on the circulation in eight dogs (mean (SD)). *P < 0.05 compared with the initial 0.2-mg kg⁻¹ min⁻¹ propofol infusion rate

<table>
<thead>
<tr>
<th>Infusion rate of propofol (mg kg⁻¹ min⁻¹)</th>
<th>0.2</th>
<th>0.3</th>
<th>0.4</th>
<th>0.5</th>
<th>0.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beat min⁻¹)</td>
<td>129 (23)</td>
<td>119 (14)</td>
<td>115 (11)*</td>
<td>112 (7)*</td>
<td>116 (14)*</td>
</tr>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>120 (17)</td>
<td>109 (10)</td>
<td>95 (11)*</td>
<td>81 (10)*</td>
<td>95 (15)*</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mm Hg)</td>
<td>88 (15)</td>
<td>78 (11)</td>
<td>67 (12)*</td>
<td>51 (9)*</td>
<td>60 (12)*</td>
</tr>
<tr>
<td>LVVEDP (mm Hg)</td>
<td>4.5 (1.9)</td>
<td>4.1 (1.9)</td>
<td>2.9 (1.4)*</td>
<td>3.1 (1)</td>
<td>3.4 (1.2)</td>
</tr>
<tr>
<td>LV (+ dP/dt max) (mm Hg s⁻¹)</td>
<td>1863 (169)</td>
<td>1563 (302)*</td>
<td>1338 (220)*</td>
<td>1087 (247)*</td>
<td>1400 (346)*</td>
</tr>
<tr>
<td>LV (- dP/dt max) (mm Hg s⁻¹)</td>
<td>1838 (262)</td>
<td>1638 (177)</td>
<td>1412 (203)*</td>
<td>1137 (256)*</td>
<td>1528 (377)*</td>
</tr>
<tr>
<td>Cardiac output (litre min⁻¹)</td>
<td>2.13 (0.6)</td>
<td>1.86 (0.54)</td>
<td>1.78 (0.58)*</td>
<td>1.48 (0.62)*</td>
<td>1.61 (0.46)*</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>16.5 (3.5)</td>
<td>15.8 (4.5)</td>
<td>15.6 (5.3)</td>
<td>13 (5.1)*</td>
<td>14.8 (3.4)*</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyn s cm⁻²)</td>
<td>4000 (1500)</td>
<td>4200 (1700)</td>
<td>3800 (1500)</td>
<td>3800 (1700)</td>
<td>3700 (800)</td>
</tr>
<tr>
<td>Aortic blood acceleration (ml s⁻¹)</td>
<td>5653 (1390)</td>
<td>4728 (1836)*</td>
<td>4196 (1789)*</td>
<td>3138 (1452)*</td>
<td>3834 (1354)*</td>
</tr>
<tr>
<td>Coronary perfusion pressure (mm Hg)</td>
<td>83 (14)</td>
<td>74 (10)</td>
<td>64 (11)*</td>
<td>48 (9)*</td>
<td>57 (12)*</td>
</tr>
<tr>
<td>Coronary blood flow (ml min⁻¹/100 g)</td>
<td>36.3 (13.6)</td>
<td>30.8 (13.6)</td>
<td>24.7 (13.5)*</td>
<td>21.0 (16)*</td>
<td>24.9 (14.8)*</td>
</tr>
<tr>
<td>Peak hyperemic flow (ml min⁻¹/100 g)</td>
<td>123.3 (46.9)</td>
<td>97.8 (38.5)*</td>
<td>73.9 (30.4)*</td>
<td>50.8 (24.9)*</td>
<td>58.9 (30.7)*</td>
</tr>
<tr>
<td>Coronary vascular resistance (mm Hg ml⁻¹ min⁻¹/100 g)</td>
<td>2.8 (1.7)</td>
<td>3.0 (1.9)</td>
<td>3.5 (2.2)</td>
<td>3.3 (1.9)</td>
<td>2.9 (1.8)</td>
</tr>
</tbody>
</table>

For infusion rate dependent effects, the data were analysed using two-way analysis of variance and Duncan's multiple range test and analysis of variance for repeated measures. For drug concentration related effects, the data were subjected to linear regression analysis. P < 0.05 was considered significant. All values are given as mean (SD).

RESULTS

Blood concentrations of propofol obtained at increasing infusion rates are shown in figure 1 as individual values. Each point represents the average of the two blood samples taken at each of the five infusion rates. The samples were taken before and after haemodynamic recordings at the end of each infusion period (10 min apart). The mean percentage difference between paired samples was 19.5 (SD 16.7)%. The coefficient of variation of the assay over the same concentration range was 5-12%. Median propofol concentrations at the four increasing infusion rates were 8.25, 13.25, 18.9 and 31.45 µg ml⁻¹. Whereas there was an approximately linear relationship between drug input and measured concentrations at the three slowest infusion rates, the observed propofol concentration at 0.5 mg kg⁻¹ min⁻¹ was significantly different from the predicted value, and there was a wide range of values at this infusion rate (15.3-36.3 µg ml⁻¹). Because of this variability, we have analysed the data in two separate ways: with respect to infusion rate and with respect to individual drug concentration.

Global haemodynamics

The global haemodynamic data are shown in table I. Control values throughout were taken as those obtained with the initial 0.2-mg kg⁻¹ min⁻¹ infusion rate of propofol.

![Graph showing blood concentrations of propofol obtained with increasing infusion rates. Each point represents the mean of two measurements (10 min apart) during continuous infusion in eight dogs. At the 0.4- and 0.2- (recovery) mg kg⁻¹ min⁻¹ infusion rates, there are only seven propofol concentration data points.](image-url)
Increasing infusion rates of propofol decreased heart rate: 0.3-, 0.4- and 0.5-mg kg$^{-1}$ min$^{-1}$ infusion rates produced reductions in heart rate of 7.8 %, 10.9 % and 13.2 %, respectively. These reductions were significantly different from control for the 0.4- and 0.5-mg kg$^{-1}$ min$^{-1}$ infusion rates. Both SAP and DAP were reduced by increasing propofol infusion rates; the reductions were statistically significant from control at 0.4 and 0.5 mg kg$^{-1}$ min$^{-1}$. Infusion rates of 0.3, 0.4 and 0.5 mg kg$^{-1}$ min$^{-1}$ reduced SAP by 9.2 %, 20.8 % and 32.5 %, respectively, and DAP by 11.4 %, 23.9 % and 42 %, respectively.

LVEDP decreased with increasing propofol infusion rates, the difference reaching statistical significance with the 0.4-mg kg$^{-1}$ min$^{-1}$ infusion rate. LV dP/dt$_{max}$ decreased significantly with increasing infusion rates of propofol: 0.3-, 0.4- and 0.5-mg kg$^{-1}$ min$^{-1}$ infusion rates reduced LV dP/dt$_{max}$ by 15.8 %, 32.6 % and 42.1 %, respectively. Further evidence that propofol depressed myocardial contractility was provided by the significant reductions in aortic blood acceleration produced with increasing infusion rates. Reductions of 16.4 %, 25.8 % and 44.5 % occurred with infusion rates of 0.3, 0.4 and 0.5 mg kg$^{-1}$ min$^{-1}$, respectively. Stroke volume (SV) also decreased with increasing infusion rates of propofol, although this reduction only reached statistical significance at the greatest rate of infusion of propofol, at which SV was reduced by 21.2 %. As the reduction in SV was associated with a reduction in heart rate, cardiac output (CO) decreased with increasing infusion rates. These reductions were significant for the 0.4- and 0.5-mg kg$^{-1}$ min$^{-1}$ infusion rates (16.4 % and 30.5 %, respectively). Propofol significantly reduced the maximum rate of negative left ventricular pressure change ($-\text{LV dP/dt}_{max}$) with the 0.4- and 0.5-mg kg$^{-1}$ min$^{-1}$ infusion rates, by 23.2 % and 38.1 %, respectively. SVR was essentially unchanged by increasing propofol infusion rates.

During the recovery period at an infusion rate of 0.2 mg kg$^{-1}$ min$^{-1}$, heart rate, SAP and DAP decreased significantly compared with the initial 0.2-mg kg$^{-1}$ min$^{-1}$ infusion rate—by 10.1 %, 20.8 % and 31.8 %, respectively. Myocardial contractility and CO decreased also compared with control values (24.8 % and 24.4 %, respectively).
In this study, increasing arterial baroreceptors which modify heart rate and induce marked resetting of the heart rate baroreflex system were used to allow slower heart rates despite decreases in arterial pressure; this is thought to be caused by increased vagal tone (or a sympatholytic effect, or both) [5]. A direct effect of propofol on the spontaneous rate of isolated atria, attributed to a reduction in Ca²⁺ fluxes has also been reported [18].

Arterial pressure was reduced by increasing infusion rates of propofol. This may be the result of reduced preload, depressed myocardial contractility or decreased systemic vascular resistance. High infusion rates of propofol resulted in decreases in EDL and LVEDP, which indicate a reduction in preload. This is consistent with observations by Goodchild and Serrao [9]. In addition, high infusion rates of propofol caused reductions in LV dP/dtmax, aortic blood acceleration and stroke volume, indicative of depressed contractility and global cardiac performance. However, there was no apparent effect of propofol on SVR. This is at variance with reports of decreases in SVR [2, 7, 9, 16], perhaps because of differences in methodology and basal vascular tone.

The maximal rate of pressure decline after end-diastolic ejection may be used as an index of ventricular relaxation [19]. A dose-dependent reduction indicates that propofol impaired ventricular relaxation. This may have been caused by a decrease in loading, as this is one of the determinants of relaxation. Another possible explanation is an effect of propofol on the inactivation process of cardiac contraction itself. This may result when calcium uptake into the sarcoplasmic reticulum is blocked, calcium leaks from these stores, the myocytes are unable to extrude the excess calcium, or when the affinity of the troponin for calcium is excessive. Indeed, it has been shown that propofol reduces calcium influx across the sarcolemma and the “tail” current that represents calcium-stimulated release of calcium from intracellular stores [10].

Although the coronary circulation is auto-regulated, interventions which impair the function of smooth muscle in coronary vessels may attenuate local coronary flow regulation. In this study, regression analysis revealed a linear relationship between CPP and resting coronary blood flow (fig. 3). As propofol decreases myocardial oxygen demand, this indicates that propofol does not significantly affect coronary autoregulation.

Despite the dose range being only 2.5-fold, there was an 8-fold range in blood concentration of propofol. This reflects the kinetic variability seen in most studies in man and in experimental animals [13, 20]. Over this blood propofol concentration range (4.2–36.2 μg ml⁻¹), there were significant negative correlations between drug concentration and arterial pressure and left ventricular contractility. There was no concentration-related alteration in coronary vascular resistance, the reduction in coronary blood flow being a reflection of the reduced myocardial oxygen consumption associated with the reductions in systolic pressure and contractility. Increasing concentrations of propofol, however, resulted in attenuation of the hyperaemic response (fig. 3), that may be attributed to the reduction in CPP. The coronary vasodilator reserve, the difference between resting arterial coronary blood flow and flow measured during maximal vasodilatation
Differences in wall tension may play a role in determining regional differences in %SS, while the base did not. Differences in wall tension may be anticipated that the basal region would shorten less but develop more tension during each contraction, while the apical region would develop less tension but shorten more.

In this study, the blood concentrations of propofol for a given infusion rate were greater than those reported by Naeije and colleagues [27] in closed-chest dogs. After the infusion rate of propofol had been returned to control values for the 1-h recovery period, blood concentrations of propofol were increased compared with those during the initial "control" propofol infusion rate (median 13.8 \( \mu \text{g ml}^{-1} \) vs 8.25 \( \mu \text{g ml}^{-1} \)). The smaller cardiac output during this recovery period may partially explain these alterations in propofol disposition (fig. 1). The depression of contractility after recovery was greater than that obtained during the 0.3-mg kg\(^{-1}\) min\(^{-1}\) infusion rate when blood concentrations of propofol were similar. These results suggest that, when myocardial depression has occurred following a prolonged infusion of propofol, increased blood concentrations of propofol, or both, recovery is delayed. Similar observations have been reported by Coetzee and colleagues [15] using an open-chested pig model.

While historical comparisons have to be considered with great caution, the effects of the greatest rate of infusion of propofol on mean arterial pressure were similar to those we have reported for 1.5 MAC of halothane, isoflurane and enflurane and the reductions in LV \( \frac{dP}{dt}_{\text{max}} \) were similar to those reported with 1 MAC halothane, 1.5 MAC isoflurane and 1.25 MAC enflurane [25, 28, 29]. Thus the greatest rate of infusion of propofol was associated with depression of cardiac function corresponding, at the most, to 1.5 MAC of inhalation anaesthetics, while this infusion rate was 2.5 times the minimum infusion rate necessary for the conduct of the study.

In conclusion, both reduced preload and depressed myocardial contractility contribute to the reduction in arterial pressure caused by propofol, systemic vascular resistance remaining unchanged. Increased rates of infusion of propofol also impaired relaxation. Autoregulation of coronary blood flow was maintained. Recovery was relatively slow after exposure to increased rates of infusion of propofol and may not parallel the anticipated decrease in anaesthetic concentrations.

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**REFERENCES**

PROPOFOL AND LEFT VENTRICULAR FUNCTION


