HAEMODYNAMIC AND HEART RATE REFLEX RESPONSES TO PROPOFOL IN THE RABBIT

Comparison with Althesin

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Propofol (Diprivan, ICI) provides satisfactory anaesthesia and its pharmacokinetic profile makes it suitable for use by continuous infusion [1,2]. However, the pattern of haemodynamic changes in response to the administration of propofol is complex. In clinical studies propofol has been reported to produce decreases in arterial pressure, cardiac output (CO) and total peripheral vascular resistance (TPR) of varying degree, whereas heart rate was maintained [3–6]. In some circumstances more marked arterial hypotension has occurred and this may limit the use of propofol for major surgery [7]. The presence of other anaesthetics and the nature of ventilatory control influence such responses.

In the absence of other anaesthetics, single doses or infusions of propofol have been reported to decrease MAP and cardiac output by less than 20% [5,6], whereas greater decreases occurred with propofol plus nitrous oxide [7,8]. The decrease in systemic vascular resistance with propofol appears to be significantly greater than that following the administration of Althesin or thiopentone [4,8]. Although the mechanism of the decrease in resistance is unknown, studies in the isolated cat hind-limb suggest that 2–6 diisopropyl phenol formulated in Cremophor had some direct vasodilator activity [9]. An alternative explanation is that propofol may alter baroreceptor function, resulting in reduced sympathetic vascular tone. However, at least some baroreceptor-mediated responses may be well preserved during propofol anaesthesia in man [10].

SUMMARY

Propofol was administered to eight rabbits by constant i.v. infusion at 0.2, 0.4 and 0.6 mg kg\(^{-1}\) min\(^{-1}\) to produce light sedation. The lowest dose was compared with an infusion of Althesin 0.1 mg kg\(^{-1}\) min\(^{-1}\). The rabbits had been previously implanted with aortic and vena caval perivascular balloon cuffs to examine the baroreceptor–heart rate reflex and an aortic thermistor catheter for cardiac output (CO) measurements. A silastic catheter was placed in the pericardial sac so that the cardiac nerves could be blocked with local anaesthetic. Mean arterial pressure (MAP) was well maintained with all anaesthetic infusions. At the lower doses of propofol, CO increased by 20% (P < 0.01) with a corresponding decrease in total peripheral resistance (TPR). However, CO and TPR were not changed significantly by Althesin. Both anaesthetics induced a similar tachycardia. Cardiac nerve blockade did not abolish the different CO and TPR responses observed for the two agents. A dose-related reduction in the range and gain of the baroreceptor–heart rate reflex was observed with propofol (P < 0.05). The pattern of alteration of the reflex curve, however, differed between the two anaesthetics and the vagal efferent component was more resistant to blockade with propofol. The relative preservation of baroreceptor reflex responses, and the reduction in TPR by a reduction of resting constrictor tone, suggest propofol may have significant clinical advantages when used as a sedative infusion.

It is unclear from clinical data whether the hypotensive effects of propofol are principally from direct depression of the myocardium and
vascular smooth muscle, or from effects on autonomic reflex pathways. Direct depressant actions are likely to be dose-related, but reflex effects might occur at lower sedative doses and reduce the cardiovascular margin of safety.

Since propofol closely resembles Althesin in its pharmacokinetics and likely clinical applications, the two agents were compared in the present study in the rabbit. The experiments were designed to study haemodynamic and reflex responses to propofol using techniques that would not be tolerated in human subjects. Chronically implanted balloon cuffs were used to manipulate arterial pressure and determine baroreceptor-heart rate reflex function. Furthermore, in the same animals, it was possible to assess the effect on haemodynamics of temporarily denervating the heart. This was achieved by injecting local anaesthetic via a chronic pericardial catheter [11]. These techniques enabled an analysis of the role of the cardiac nerves and baroreceptor reflexes in maintaining cardiac output and total peripheral resistance during anaesthesia.

MATERIALS AND METHODS

Investigations were in eight cross-bred rabbits of either sex, weighing 2.4–3.1 kg. Preliminary operations were performed after induction of anaesthesia with thiopentone, tracheal intubation and ventilation with an air–halothane mixture.

At the first operation a thermistor catheter was placed in the infra-renal aorta via the iliolumbar artery [12]. A right-sided thoracotomy was also performed and an inflatable cuff placed around the inferior vena cava. At a second operation 2 weeks later, a left thoracotomy was performed and a cuff placed on the descending thoracic aorta. A small silastic catheter was also inserted into the pericardial sac and sutured in place. A disc of nylon was used to seal the opening in the pericardium. A further 2 weeks recovery was allowed before the start of the definitive investigation.

Catheters were inserted in a central ear artery and vein before each study under local anaesthesia (0.5 % lignocaine). A central venous catheter was also introduced via an external jugular vein. Tubing connecting to the perivascular balloons and the thermistor wires was buried subcutaneously between experiments.

Each rabbit was studied on three separate days using different anaesthetic infusions:

1. low-dose propofol: 1.5-mg kg⁻¹ bolus + 0.2 mg kg⁻¹ min⁻¹ i.v.;
2. cumulative dose propofol 1.5 mg kg⁻¹ + 0.2, 0.4 and 0.6 mg kg⁻¹ min⁻¹;
3. Althesin 1 mg kg⁻¹ + 0.1 mg kg⁻¹ min⁻¹.

A random order was used and at least 2 days allowed for recovery between experiments. The dose of Althesin used was known from previous rabbit studies to produce light anaesthesia with loss of eyelash and righting reflexes, but without significant ventilatory depression or loss of the corneal reflex. This had been found to be suitable for the assessment of autonomic reflexes without significant direct cardiovascular depression [13]. The doses of propofol were chosen according to the reported relative potencies of propofol and Althesin in man [4,14]. Arterial blood-gas tensions were measured randomly, but were not altered significantly by any of the anaesthetic infusions.

Arterial pressure and right atrial pressure (RAP) were measured with Hewlett-Packard transducers and recorded on a “Gould” chart recorder. Heart period (HP, pulse interval) was also measured directly from the arterial pulse with a pulse interval meter. All measurements of cardiac output were averaged from six thermodilution curves and total peripheral resistance was calculated using mean arterial pressure (MAP) and right atrial pressure. Measurements were made in the awake animal and after the anaesthetic had been infused for 40, 60 and 80 min.

Baroreceptor reflex curves, relating MAP to pulse interval, were derived from graded inflations of the aortic and IVC balloon cuffs to increase and decrease MAP, respectively [15]. In individual animals, reflex measurements were based on a total of 12 balloon inflations over a period of 15–20 min. Each inflation was maintained for about 40 s and the heart rate response in the final 10 s recorded. Sigmoid curves were fitted to these data using a logistic transformation and described by four variables (table II, fig. 2): lower plateau, heart period range, average gain and arterial pressure at middle of heart period range (AP₅₀). These variables were averaged to obtain pooled data from the group of animals.

Temporary blockade of efferent and afferent cardiac nerves was achieved by injection of 1 ml of 2% procaine via the pericardial catheter. This was repeated after 10–15 min. The efficacy of the block was confirmed if the heart rate responses to balloon inflations were abolished [11]. Injections
of 1 ml of physiological saline intrapericardially or of 2% procaine 1 ml systemically produced no detectable response.

After insertion of the catheters, the rabbits rested in an experiment box for 20 min before measurement of control circulatory variables and baroreceptor–heart rate reflex curves. The relevant anaesthetic was then infused for 60 min, the baroreflex curve being repeated between 45 and 60 min. After 60 min of anaesthesia with either low-dose propofol or Althesin, the cardiac nerves were blocked with procaine and the infusion of the of the anaesthetic continued for 20 min. In the experiments in which cumulative doses of propofol were studied, the rate of infusion was doubled at 40-min intervals.

Two-way analysis of variance was performed on the haemodynamic data and the indices of baroreceptor reflex activity. Orthogonal partitioning of the treatments sum of squares was used to compare the effects of the anaesthetic infusions and cardiac blockade within animals [16]. The results are expressed with either the standard error of the mean, or standard error of the difference, obtained from the analysis of variance.

RESULTS

The infusions of Althesin and the two lower doses of propofol produced similar levels of light anaesthesia. There was loss of the eyelash and righting reflexes, but a persisting response to noxious stimuli and a corneal reflex. The highest propofol dose induced deeper anaesthesia with a lack of response to noxious stimuli, but no significant alteration in blood-gas tensions.

Circulatory responses to anaesthesia

Control values for MAP, RAP, CO, TPR and heart rate did not vary significantly in the same animal on the three experiment days, indicating that resting conditions were achieved and that there were no lasting circulatory effects from any treatment.

Propofol did not alter MAP at the two lower infusion rates, but at 0.6 mg kg⁻¹ min⁻¹ there was a small reduction of 7±4 mm Hg (table I). However, CO was increased significantly (P < 0.05) by 30±6% and 23±6% with propofol infusions of 0.2 and 0.4 mg kg⁻¹ min⁻¹, respectively. This was associated with a corresponding decrease in TPR. When the infusion of propofol was increased to 0.6 mg kg⁻¹ min⁻¹, CO decreased, although TPR remained less than the control values obtained in the awake animal. Heart rate increased progressively with increasing doses of propofol, to be 24±6% above control at the highest infusion rate (P < 0.01).

The responses to propofol 0.2 mg kg⁻¹ min⁻¹ and Althesin 0.1 mg kg⁻¹ min⁻¹ are compared in figure 1. Neither significantly altered MAP and there were similar increases in heart rate (18±6% and 20±6%). The changes in CO and TPR were different during propofol compared with Althesin infusion (P < 0.01) (fig. 1). Propofol increased CO after 40 and 60 min by 19% and 15%, respectively, associated with a reduction in TPR. However, CO and TPR were not significantly changed during the infusion of Althesin.

Blockade of the cardiac nerves

Intra-pericardial procaine during infusions of propofol or Althesin reduced heart rate to values similar to (pre-anaesthesia) control (P < 0.01) (fig. 1); MAP was not altered significantly. CO was reduced in both groups (P < 0.01), but the difference in TPR was maintained, remaining below control in the propofol-treated animals with cardiac block, but being significantly in-

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**TABLE I. Average circulatory variables (n = 6) for the awake animal (control) and after 40-min periods of propofol infusion. Standard error of the mean (SEM) represents the within animal variance for the effects of anaesthesia derived from two-way analysis of variance as (error mean square/n)**

<table>
<thead>
<tr>
<th>Propofol infusion (mg kg⁻¹ min⁻¹)</th>
<th>Control</th>
<th>0.2</th>
<th>0.4</th>
<th>0.6</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>87</td>
<td>87</td>
<td>89</td>
<td>80</td>
<td>2.9</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>0.9</td>
<td>0.8</td>
<td>-0.1</td>
<td>0.3</td>
<td>0.8</td>
</tr>
<tr>
<td>CO (ml min⁻¹)</td>
<td>834</td>
<td>1036</td>
<td>1010</td>
<td>847</td>
<td>52</td>
</tr>
<tr>
<td>TPR (units)</td>
<td>104</td>
<td>84</td>
<td>88</td>
<td>91</td>
<td>5.5</td>
</tr>
<tr>
<td>HR (beat min⁻¹)</td>
<td>220</td>
<td>256</td>
<td>269</td>
<td>273</td>
<td>13.6</td>
</tr>
</tbody>
</table>
creased in the Althesin group with cardiac block ($P < 0.05$).

**Baroreceptor—heart rate reflex**

Sigmoid curves relating MAP to heart period (HP, pulse interval) were fitted to the data from individual experiments. The averaged variables (table II) were then used to construct the curves in figure 2. The indices of the control baroreflex curves, obtained in the awake animals, showed no significant differences between each of the three experiment days. The (control) curve indices in table II are, therefore, averaged from the three experiments.

The infusions of propofol produced a dose-related reduction in the heart period range of the MAP-HP curve from 256 to 108 ms ($P < 0.01$) (fig. 2). This was a result of alterations in the

![Figure 1](https://example.com/fig1.png)

**Figure 1.** Circulatory responses to 80-min infusions of propofol and Althesin. The cardiac nerves were blocked with 2% procaine after 60 min. MAP = Mean arterial pressure; ΔCO = change in cardiac output from control; ΔTPR = change in total peripheral resistance; HR = heart rate. Error bars indicate SEM from analysis of variance. Vertical dashed line indicates cardiac block.

| Table II. Average baroreceptor—heart rate reflex variables (n = 6). Standard error of mean (SEM) based on within-animals variance from analysis of variance. $AP_{50}$ = Arterial pressure at mid heart period range (HP range) |
|-----------------|-----------------|-----------------|-----------------|
|                 | HP range        | Av. gain         | $AP_{50}$       | Lower plateau   |
|                 | (ms)            | (ms (mm Hg)$^{-1})$ | (mm Hg)        | (ms)            |
| Av. control     | 256             | 14.5             | 82.3            | 185             |
| Propofol        |                 |                  |                 |                 |
| 0.2 ml kg$^{-1}$ min$^{-1}$ | 205             | 10.7             | 82.5            | 175             |
| 0.4 ml kg$^{-1}$ min$^{-1}$ | 141             | 6.8              | 81              | 180             |
| 0.6 ml kg$^{-1}$ min$^{-1}$ | 108             | 3.3              | 80.2            | 188             |
| Althesin        | 120             | 1.7              | 93              | 182             |
| SEM             | 28.1            | 1.1              | 2.4             | 8.6             |
upper plateau of the curve; that is, the vagal efferent component of the reflex. Reflex gain was reduced at the higher doses of propofol infusion by 7.7 and 11.2 ± 1.6 ms (mm Hg⁻¹) (P < 0.05).

The infusion of Althesin reduced the gain and range of the reflex (P < 0.05) to values similar to those after infusion of propofol 0.6 mg kg⁻¹ min⁻¹. There was also a small increase of 11 ± 3 mm Hg in the median arterial pressure (P < 0.05). None of the anaesthetic infusions significantly influenced the lower plateau of the curve; that is, the maximum tachycardia.

DISCUSSION

The haemodynamic responses to propofol in the rabbit have important similarities with those described in clinical studies. In the present study, total peripheral resistance was reduced at each dose of propofol and this was the principal difference between the effects of propofol and Althesin. A reduction in cardiac output has generally been reported in man. However, the doses of propofol used in these clinical studies were selected so as to provide deeper levels of anaesthesia, and such doses are likely to depress myocardial function directly. In contrast in the present study, the haemodynamic effects of propofol were examined in animals in the absence of any influences of surgical procedures or other drugs likely to cause myocardial depression. MAP and CO were reduced in the rabbit as the dose of propofol was increased, suggesting that a dose-related direct depression of cardiovascular function also occurs in this species. The increase in heart rate after propofol appears to contrast with the reported responses in man. However, the changes in the baroreceptor–heart rate reflex after propofol indicate that the maximum bradycardia and location of the curve are only slightly changed. Therefore, the higher resting heart rate after propofol in the rabbit, compared with results in clinical studies, may only reflect a different balance of vagal and sympathetic tone in the absence of surgery.

Tachycardia during the infusion of Althesin is caused by both reduction of vagal tone and increased sympathetic activity [13]. Cardiac denervation reduced resting heart rate by similar amounts during the two anaesthetic infusions, suggesting that there had been a comparable increase in cardiac sympathetic activity in each case before blockade with procaine. The smaller increase in heart rate after 40 min of propofol compared with Althesin probably reflects a lesser degree of vagal block with propofol, as found in the baroreceptor–heart rate reflex responses.

Propofol was also much less potent than Althesin in causing depression of baroreceptor–heart rate reflex responses. In previous studies in the rabbit we reported that Althesin caused less reflex depression than equivalent doses of thiopentone or ketamine. The latter appeared to act more proximally on the baroreflex arc and to alter both vagal and sympathetic responses [17]. It is likely that propofol and Althesin also act on reflex pathways at different central nervous system sites, as there were qualitative differences in their effects on the baroreflex curves. No shift in the location of the curve was seen with propofol and the reflex range was reduced independently from the gain at the lower propofol doses. However, neither propofol nor Althesin altered the sympathetic efferent component of the heart rate responses, in contrast to comparable doses of other anaesthetics.

Cardiac efferent and afferent nerves can be blocked rapidly and reversibly by the intrapericardial injection of local anaesthetic, without significant systemic effects [11]. Complicating central nervous system or peripheral vascular effects that might follow the systemic infusion of receptor blocking drugs are also avoided. Loss of
the cardiac sympathetic responses after intrapericardial procaine reduced CO by similar amounts during propofol and Althesin anaesthesia and in each case, MAP was maintained by an increase in TPR. Therefore, reflex peripheral vasoconstrictor responses could still be induced following low doses of either of these anaesthetics. This is in keeping with the lesser degree of depression of the heart rate reflexes with these agents compared with thiopentone or ketamine.

 Increases in TPR during low-dose anaesthetic infusions can result from depression of the afferent limb of arterial baroreceptor reflexes and disinhibition of vasoconstrictor tone [13]. Input from low pressure cardiac receptors, however, is also thought to modulate arterial baroreceptor responses [18] and effects on this input might account for the differences in vasoconstrictor tone during propofol compared with Althesin anaesthesia. A significant direct vasodilator action of propofol in the doses used is unlikely, so the observed decrease in TPR with propofol in these experiments probably reflects reflex changes in sympathetic tone. It is likely that the input of cardiac afferents was involved in this reflex as, after blockade of both cardiac efferents and afferents, cardiac output and total peripheral resistance returned almost to pre-anaesthetic resting values.

 These investigations suggest that the infusion of propofol in sedative doses results in a beneficial reduction in cardiac afterload with preservation of autonomic reflex function. However, when dosage is increased and reflexes are blocked by the administration of other drugs, direct depressant actions may be unmasked. This animal study suggests that the ideal clinical use of propofol may be as a supplement to regional anaesthesia rather than as a component of general anaesthesia for major surgery.

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