J Anesth (1999) 13:34–39

Journal of
Anesthesia

Cardiac effects of propofol and its interaction with autonomic nervous system in isolated, cross-circulated canine atria

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Abstract
Purpose. The effects of propofol on sinoatrial pacemaker activity and myocardial contractility and its interaction with the autonomic nervous system were investigated in isolated, cross-circulated right atrial canine preparations.
Methods. An isolated right atrial preparation was perfused with heparinized arterial blood from an anesthetized support dog and changes in atrial rate and atrial contractile force were recorded.
Results. Propofol (30–1000 μg) and thiopental (30–1000 μg), injected into the sinus node artery of the isolated atrium, induced dose-dependent decreases in atrial rate and contractile force. The negative chronotropic and inotropic effects of propofol were greater than those of thiopental. The propofol-induced negative chronotropic and inotropic responses were not inhibited by atropine. Propofol had no effects on the cardiac responses to acetylcholine, norepinephrine, and the intracardiac parasympathetic nerve stimulation which activates ganglionic nicotinic acetylcholine receptors.
Conclusion. These results indicate that: (a) propofol directly depresses sinoatrial pacemaker activity and myocardial contractility, (b) the negative chronotropic and inotropic effects of propofol do not involve activation of muscarinic receptors, and (c) propofol has little interaction with the autonomic nervous system at the effector site.

Key words: Propofol, Chronotropy, Inotropy, Muscarinic receptor, Dog heart

Introduction

Induction of anesthesia with propofol is generally associated with decreases in arterial blood pressure and minimal change in heart rate [1–3]. Propofol decreased myocardial contractile force in humans [4], in isolated mammalian hearts [5,6], and in chronically instrumented dogs [7], suggesting that the negative inotropic effect of propofol contributes to the decreases in arterial blood pressure. On the other hand, lack of compensatory tachycardia in the presence of hypotension can be attributed to a decrease in baroreflex sensitivity [8,9] or a resetting of baroreceptors to allow a slower heart rate despite the decreased arterial blood pressure [10]. Thus, it is assumed that propofol reduces sympathetic outflow and exerts a central vagotonic effect. However, interactions between propofol and the autonomic nervous system at the effector site have not been well documented.

Propofol prolonged the atrioventricular conduction time in isolated guinea pig hearts, which was inhibited by atropine [11]. However, whether propofol affects other cardiac functions, i.e., chronotropic and inotropic actions, through the parasympathetic neurotransmission, has not been clarified. The first aim of this study was to re-evaluate the direct effects of propofol on pacemaker activity and myocardial contractility and to determine whether propofol-induced chronotropic and inotropic effects are mediated through the parasympathetic neurotransmission. The second aim was to examine how propofol modifies cardiac responses to sympathetic and parasympathetic stimuli at the effector site. To achieve these aims, we used isolated, cross-circulated atrial canine preparations, which allowed us to study the direct chronotropic and inotropic effects of propofol, with thiopental as control, and its interaction with the autonomic nervous system [12,13].

Materials and methods

The experimental protocol was approved by our Institutional Animal Welfare Committee.

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Received for publication on June 1, 1998; accepted on September 20, 1998

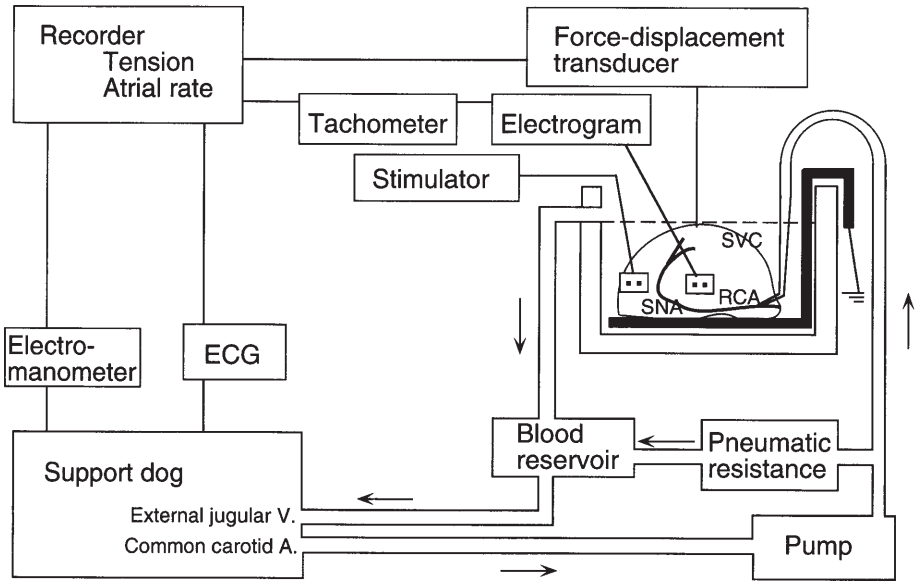

Fig. 1. Isolated, cross-circulated right atrial preparation. *RCA*, right coronary artery; *SNA*, sinus node artery; *SVC*, superior vena cava; *ECG*, electro-cardiogram; *V*, vein; *A*, artery

An isolated right atrial preparation was perfused with arterial blood from a support dog. The details of these preparations have been described previously [12,13]. Figure 1 shows a diagram of the experimental set-up and measurements.

The support dogs, mongrels weighing 12–35 kg, were anesthetized with sodium pentobarbital, 30 mg·kg^{-1} i.v., and artificially ventilated with room air with a respirator (model 55–715; Harvard Apparatus, South Natick, MA, USA). The systemic blood pressure of the support dog was measured from the cannulated right femoral artery with a pressure transducer (AP601G; Nihon Kohden, Tokyo, Japan), and heart rate was measured with a cardiotachometer (AT601G; Nihon Kohden) triggered by the R wave of the electrocardiograph. The common carotid artery and the external jugular vein were cannulated for the perfusion to the isolated preparation. Sodium heparin, 500 USP units·kg^{-1} i.v., were administered at the beginning of the perfusion, and 200 USP units·kg^{-1} was given each hour thereafter.

Isolated right atrial preparations were obtained from other mongrel dogs (weighing 7–16 kg). Each dog was anesthetized with sodium pentobarbital, 30 mg·kg^{-1} i.v. and 200 USP units·kg^{-1} of i.v. sodium heparin was administered. The right atrium was then excised and immersed in cold Ringer solution at about 4°C. The wet weight of the isolated right atrial preparations varied from 5 to 13 g. The right coronary artery was cannulated and its branches to the right ventricle were ligated so that the blood could effectively circulate in the atrial muscle and the sinus node artery. The preparation was perfused with heparinized blood conducted from the common carotid artery of the support dog with the aid of a peristaltic pump (model 1210; Harvard Apparatus). A pneumatic resistance was placed in parallel with the perfusion system so that a constant perfusion pressure of 100 mmHg could be maintained. The venous effluent from the preparation was led to a blood reservoir and returned to the support dog through the external jugular vein.

Two pairs of silver electrodes were brought into contact with the epicardial surface of the isolated atrium. The first pair of electrodes placed on the atrial free wall was used to record the electrogram. The atrial rate was measured with a cardiotachometer (AT600G; Nihon Kohden) which was triggered by the atrial electrogram. The second pair of electrodes placed on the fatty tissue near the caval margin of the atrium was used to stimulate the intracardiac parasympathetic nerve fibers [14,15]. The ventricular margin of the atrium was fixed to a stainless steel bar and the preparation was placed in a cup-shaped glass container that was kept at a constant temperature of 37°C. The superior part of the atrium was connected to a force-displacement transducer (AP620G; Nihon Kohden) by a silk thread. The atrial muscle was loaded with a resting tension of 2 g. The isometric tension and atrial rate were recorded on a thermo-writing rectigraph (RTA 1200; Nihon Kohden). To study the cardiac responses to stimulation of the intracardiac parasympathetic nerve fibers, we applied steady stimulation with an electrical stimulator (SEN 7103; Nihon Kohden) with a pulse duration of <0.05 ms, at 10 V, at a frequency of 10 Hz for 10 s. This stimulation intensity with a narrow pulse duration was subthreshold

for activation of the atrial muscle cells, pacemaker cells, and sympathetic nerves [14,15].

We conducted two series of experiments. In the first series, we investigated the direct effects of propofol on atrial rate and atrial myocardial contractility . Propofol, at doses of 30–1000 μg, was injected into the sinus node artery of the isolated atrial preparation ($n = 8$). The propofol was used in the form of a commercial 10% intralipid emulsion formula (Zeneca, Osaka, Japan). We chose thiopental as the drug of reference and examined the chronotropic and inotropic effects of thiopental at the same doses as propofol. We also examined the chronotropic and inotropic effects of the propofol solvent (10% intralipid). A sufficient time for recovery was allowed between each injection of the drug. To determine whether the chronotropic and inotropic effects of propofol involve activation of muscarinic receptors, we studied the effects of atropine on the cardiac responses to propofol in six isolated atria. After control responses to propofol (1000 μg), acetylcholine (ACh, 0.05 or 0.18 μg), and intracardiac parasympathetic stimulation (IPS) were measured, atropine (5 μg) was injected into the sinus node artery of the preparation. One min later, cardiac responses to the same interventions were measured.

In the second series of experiments, to investigate interactions between propofol and the autonomic nervous system at the effector site, we investigated the effects of propofol on the responses of the isolated atrium to IPS, ACh (0.05 or 0.18 μg), and norepinephrine (NE, 0.02 or 0.05 μg) in five preparations. After control responses were measured, propofol (3 mg·kg^{-1}) was administered into the external jugular vein of the support dog, and then given as a continuous infusion at a rate of 15 mg·kg^{-1}·h^{-1}. Ten min after the propofol infusion was started, cardiac responses to the same interventions were measured.

Data values are shown as maximal percentage changes from predrug values and are expressed as mean ± SEM. The data were analyzed with analysis of variance and Bonferroni's method for multiple comparisons of data. Student's *t*-test was used for comparisons between two groups. *P* values less than 0.05 were considered statistically significant.

Results

Direct effects of propofol and thiopental in isolated atrial preparations

When propofol and thiopental at doses of 30–1000 μg were injected into the sinus node artery of the isolated atrial preparation, atrial rate and contractile force decreased in a dose-dependent manner ($P < 0.001$, Fig. 2).

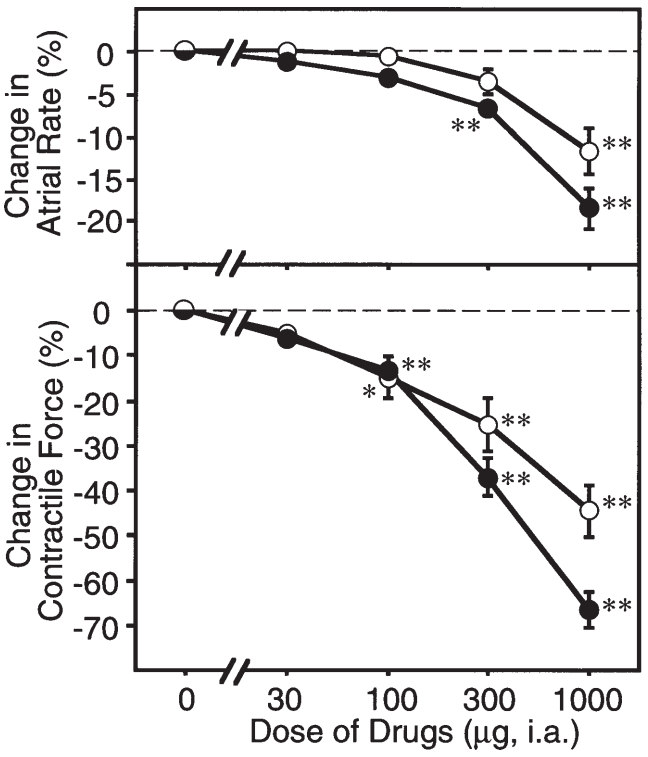

Fig. 2. Dose-response curves for mean maximum percent changes in chronotropic (*upper panel*) and inotropic (*lower panel*) responses to propofol and thiopental in eight isolated, cross-circulated atrial preparations. *Vertical bars* show SEM. $*P < 0.05$; $**P < 0.01$ compared with control values. *Dots*, Propofol; *circles*, thiopental; *i.a.*, intra arterial

The negative chronotropic and inotropic effects of propofol were greater in magnitude ($P < 0.001$) than those produced by thiopental. Propofol solvent (10% intralipid) at a volume of 100 μl (equivalent volume for 1000 μg of propofol) increased atrial contractile force by 3.3 ± 1.3% ($n = 7$), but induced no significant chronotropic responses. The baseline values for each experiment are shown in Table 1.

Effects of atropine on negative chronotropic and inotropic responses to propofol in isolated atrial preparations

The effects of atropine on the propofol-induced negative chronotropic and inotropic responses were investigated in six isolated atria. Atropine, at a dose of 5 μg, significantly ($P < 0.05$) inhibited the negative chronotropic and inotropic responses to 0.05 or 0.18 μg of ACh and those to IPS, whereas atropine did not affect the negative chronotropic and inotropic responses to 1000 μg of propofol (Table 2).

Table 1. Baseline chronotropic and inotropic values in isolated canine atrial preparations

	n	Atrial rate (beats·min^{-1})	Contractile force (g)
Experiment 1			
Propofol, Dose response	8	123 ± 8	3.3 ± 0.4
Thiopental, Dose response	8	122 ± 7	3.3 ± 0.4
Effects of atropine	6	117 ± 11	2.1 ± 0.4
Experiment 2			
Before propofol treatment	5	110 ± 6	2.5 ± 0.6
After propofol treatment	5	103 ± 7	1.9 ± 0.5

Values are means ± SEM.

Table 2. Effects of atropine (5 μg) on cardiac responses to propofol (1000 μg), acetylcholine (ACh, 0.05 or 0.18 μg), and intracardiac parasympathetic stimulation (IPS) in isolated canine atria

	Atrial rate (%)		Contractile force (%)	
	Control	Atropine treatment	Control	Atropine treatment
Propofol	−13.0 ± 2.8	−13.7 ± 2.1	−66.5 ± 3.5	−63.3 ± 5.8
ACh	−6.7 ± 2.8	0*	−74.3 ± 4.8	−2.2 ± 1.4**
IPS	−24.7 ± 6.4	0*	−57.5 ± 6.2	0**

* $P < 0.05$; ** $P < 0.01$ compared with pretreatment control values.
Values represent percent changes from control atrial rate and contractile force (mean ± SEM; $n = 6$).
Electrical stimuli were given at a pulse duration of 0.01–0.05 ms, at 10 V and 10 Hz for 10 s.

Effects of propofol on negative chronotropic and inotropic responses to intracardiac parasympathetic stimulation and ACh, and on positive chronotropic and inotropic responses to NE in isolated atrial preparations

When propofol was given at 3 mg·kg^{-1} i.v. and then infused at a rate of 15 mg·kg^{-1}·h^{-1} i.v., the heart rate and arterial blood pressure of the support dog decreased, and atrial rate and atrial contractile force decreased from 110 ± 6 to 103 ± 7 beats·min^{-1} and from 2.5 ± 0.6 to 1.9 ± 0.5 g, respectively, in five experiments. Electrical stimulation of the intracardiac parasympathetic nerves and treatment with ACh (0.05 or 0.18 μg) induced negative chronotropic and inotropic responses in the isolated atrial preparation. These responses were not affected by treatment with propofol (Table 3). NE (0.02 or 0.05 μg) induced positive chronotropic and inotropic responses in the isolated atrial preparation. These responses also were not affected by the treatment with propofol (Table 3).

Discussion

We observed dose-dependent negative chronotropic and inotropic effects of propofol and thiopental when they were injected into the sinus node artery of isolated atrial preparations. This finding indicates that both drugs directly depress sinoatrial pacemaker activity and myocardial contractility, as centrally mediated autonomic nervous tone was absent in the isolated atrial preparation. The negative chronotropic and inotropic effects of propofol were greater in magnitude than those produced by thiopental. This finding is in accordance with the study of Mulier et al. [4] in humans and that of Stowe et al. [6] in isolated guinea pig hearts. However, the results should be interpreted with caution. Since we did not measure the blood concentrations of the anesthetics, it is not certain whether the doses used here produced plasma concentrations that would be clinically relevant. Furthermore, in clinical practice, the optimal dose of thiopental for induction of anesthesia is generally accepted to be 1.6 to two times larger than that of propofol [1,3]. Therefore, we should note that, in our experimental design, we did not compare the two drugs at equipotent doses.

We found that atropine did not inhibit the negative chronotropic and inotropic responses to propofol in the isolated atrium. This result suggests that the negative chronotropic and inotropic effects of propofol do not involve the activation of muscarinic receptors. Alphin et al. [11] have shown that the negative dromotropic effect

Table 3. Effects of propofol treatment on cardiac responses to intracardiac parasympathetic stimulation (IPS), acetylcholine (ACh, 0.05 or 0.18 μg), and norepinephrine (NE, 0.02 or 0.05 μg) in isolated atria

	Atrial rate (%)		Contractile force (%)	
	Control	Propofol treatment	Control	Propofol treatment
IPS	−21.0 ± 4.1	−20.4 ± 3.8	−47.8 ± 6.5	−49.8 ± 8.6
ACh	−2.2 ± 0.9	−2.0 ± 1.5	−48.0 ± 7.5	−46.4 ± 9.4
NE	13.2 ± 2.9	14.8 ± 3.8	59.8 ± 8.9	52.2 ± 3.8

Values represent percent changes from control atrial rate and contractile force (means ± SEM; $n = 5$).
Propofol was given at 3 mg·kg^{-1} i.v. and then infused at a rate of 15 mg·kg^{-1}·h^{-1} i.v. to the support dog. Electrical stimuli were given at a pulse duration of 0.01–0.05 ms, at 10 V, and 10 Hz for 10 s.

of propofol is mediated by M2-muscarinic receptors in guinea pig isolated hearts. We are unable to provide direct evidence to account for the difference between their conclusion and ours, although it may be attributed to species differences or differences in observed cardiac effects, i.e., chronotropic and inotropic effects *vs* dromotropic effects. Previous reports from our laboratory have shown that atropine pretreatment did not affect the negative chronotropic and inotropic effects of the intravenous anesthetics, thiopental [16], midazolam [17], and ketamine [18].

Propofol is known to reduce sympathetic outflow [8,9] and to exert a central vagotonic effect [10]. However, its interaction with the autonomic nervous system at the effector site has not yet been clarified. We examined the hypothesis that propofol may have vagotonic and/or sympatholytic effects also at the effector site. However, in the present study, propofol had no effects on the cardiac responses to IPS, ACh, and NE, results that suggest that propofol has neither vagotonic nor sympatholytic effects at the effector site. Lack of vagotonic effect at the effector site is also supported by our finding that propofol had no interaction with muscarinic receptors. This finding of lack of sympatholytic effect is in contrast with the earlier findings of Hebbar et al. [19], in which β-adrenergic responsiveness was attenuated by propofol. This discrepancy may have resulted from differences in experimental design. Hebbar et al. [19] used myocytes isolated from the left ventricle of the pig and observed the effect of propofol on myocytes responses to isoproterenol added to the bath. We used isolated right atrium of a dog which was perfused with support dog blood, and NE was injected directly into the sinus node artery of the preparation. Although we did not measure the propofol blood concentrations, it is reasonable to postulate that our protocol (intravenous administration of propofol at 3 mg·kg^{-1} followed by continuous infusion at a rate of 15 mg·kg^{-1}·h^{-1}) produced a clinically relevant condition in the cross-circulated preparations [7].

In summary, our data indicate that propofol directly depresses sinoatrial pacemaker activity and myocardial contractility in isolated canine atria. Propofol-induced negative chronotropic and inotropic effects do not involve the activation of muscarinic receptors. Our findings also suggest that propofol has little interaction with the autonomic nervous system at the effector site.

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