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Short communications

Propofol decreases contractility of isolated blood-perfused left ventricular muscle in the dog

Yoshito Nagashima[1,2], Yasuyuki Furukawa[1], and Shigetoshi Chiba[1]

[1] Department of Pharmacology, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan
[2] Department of Anesthesiology, Nagano Municipal Hospital, 1333-1 Tomitake, Nagano 381-8551, Japan

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It is controversial whether propofol at clinically relevant blood concentrations has direct depressant effects on myocardial contractile force [1–10]. The present study was designed to evaluate the direct effects of propofol on myocardial contractile force. An isolated left ventricular preparation was perfused with heparinized arterial blood from an anesthetized support dog, and changes in ventricular contractile force in response to propofol and thiopental were recorded.

The experimental protocol was approved by our Institutional Animal Welfare Committee. The details of the experimental setup have been described previously [11]. The support dogs, mongrels weighing 14–35 kg, were anesthetized with sodium pentobarbital, 30 mg·kg^{-1} i.v., and artificially ventilated with oxygen and 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, and the heart rate was measured with a cardiotachometer 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., was administered at the beginning of the perfusion, and 200 USP units·kg^{-1} was given each hour thereafter. Isolated left ventricular preparations were obtained from other mongrel dogs weighing 10–13 kg. Each dog was anesthetized with sodium pentobarbital, 30 mg·kg^{-1} i.v., and 200 USP units·kg^{-1} i.v. of sodium heparin was administered. The left ventricular muscle along the anterior descending branch of the left coronary artery was then excised and immersed in cold Ringer's solution at about 4°C. The wet weight of the isolated left ventricular preparations varied from 8 to 15 g. The anterior descending branch was cannulated and 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. The isolated ventricular muscle was driven by an electrical stimulator (SEN 7103; Nihon Kohden, Tokyo, Japan) with a pulse duration of 1 ms and 4 V pulse amplitude at a frequency of 2 Hz. The superior part of the ventricle was connected to a force-displacement transducer (AP620G; Nihon Kohden) by a silk thread to measure the isometric tension. The muscle was loaded with a resting tension of 2 g.

In the first series of experiments, we investigated the changes in heart rate and arterial blood pressure of the support dog and the concomitant changes in contractile force of the isolated left ventricle ($n = 5$) when propofol (0.3–3 mg·kg^{-1}) was administered to the external jugular vein of the support dog. Each dose of propofol was given cumulatively at 10-min intervals. In the second series, to compare the negative inotropic effects of propofol and thiopental, both drugs (30–1000 μg) were injected into the anterior descending branch of the left coronary artery of the isolated ventricle ($n = 6$).

The results are shown as maximal percentage changes from predrug values and are expressed as mean ± SEM. The data were analyzed by an analysis of variance and Bonferroni's method for multiple comparisons of data. P values less than 0.05 were considered statistically significant.

Address correspondence to: Y. Furukawa
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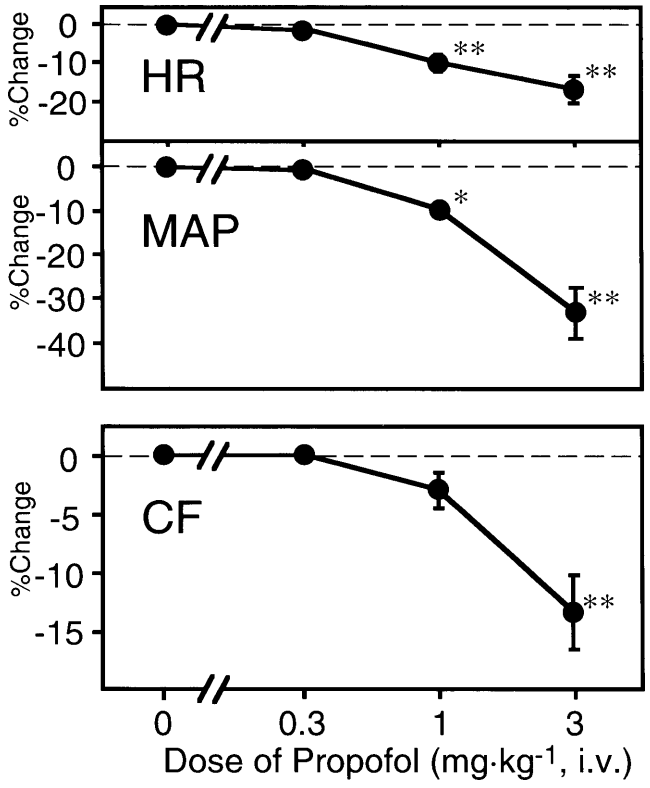

Fig. 1. Dose-response curves for mean maximum percent changes in heart rate (HR) and mean arterial pressure (MAP) of support dogs and in ventricular contractile force (CF) of isolated, blood-perfused ventricles in response to i.v. administration of propofol ($n = 5$). Baseline values: HR, 178 ± 6 beats·min^{-1}; MAP, 109 ± 12 mmHg; CF, 3.9 ± 0.6 g. Vertical bars show SEM. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with control values

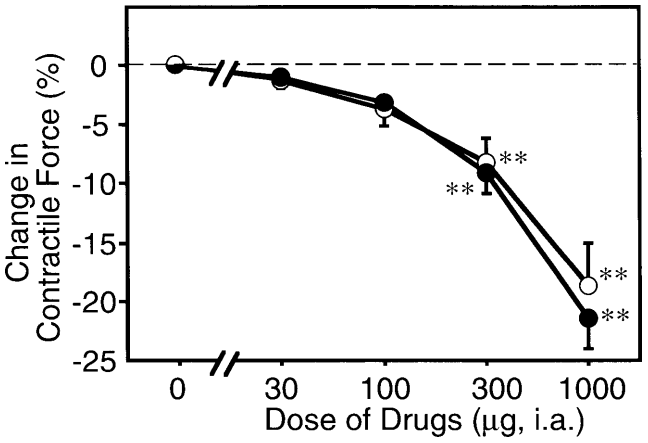

Fig. 2. Dose-response curves for mean maximum percent changes in inotropic responses to propofol and thiopental in isolated, blood-perfused ventricular preparations ($n = 6$). The baseline contractile force was 4.8 ± 1.1 g. Vertical bars show SEM. $^{**}P < 0.01$ compared with control values. *Filled circles*, propofol; *open circles*, thiopental

Propofol at a dose of 1 or 3 mg·kg^{-1} i.v. decreased heart rate and mean arterial pressure in five experiments (Fig. 1). About 2 min after i.v. injection of propofol, the contractile force of the isolated ventricle decreased. When 3 mg·kg^{-1} of propofol induced a 17 ± 3% decrease in heart rate and a 33 ± 6% decrease in mean arterial pressure of the support dog, a significant decrease in contractile force was observed (13 ± 3%, $P < 0.001$) (Fig. 1). Propofol (30–1000 μg) and thiopental (30–1000 μg), injected into the anterior descending branch of the left coronary artery of the isolated ventricle, induced dose-dependent decreases in contractile force (Fig. 2). No significant difference between the dose-response curves was observed in the contractile force of the ventricle.

The effects of propofol on myocardial contractile force have been studied in various experimental designs. However, it has not been established whether propofol at clinically relevant blood concentrations has a significant negative inotropic effect. The various conclusions cannot necessarily be attributed to differences in experimental design (in vitro *vs* in vivo). Studies in vitro had conflicting conclusions: some found a negative inotropic effect [3,5] but some did not [8,9]. Similarly, some studies in vivo found a negative inotropic effect [1,6] but some did not [4,7]. Mulier et al. [2] demonstrated reduced myocardial contractile force due to propofol in humans by using transesophageal echocardiography. On the other hand, Gelissen et al. [10] found no reduction in myocardial contractile force with clinical ranges of propofol in isolated human atrial muscle. Studies in vivo have the intrinsic problem that the influences of the autonomic nervous system, preload, and afterload cannot be ignored. Studies in vitro are suitable for evaluating direct cardiac effects of drugs, but it is critical whether the experimental condition reflects clinical circumstances. The present study can be classified as an in vitro model. Since our left ventricular preparations are perfused with oxygenated blood, the model reflects clinical circumstances more than other in vitro models in which drugs act by diffusion [3,5,9]. We recently reported that propofol directly depresses myocardial contractile force in isolated canine atria [12]. We designed this study to obtain further evidence of direct negative inotropism of propofol using ventricular preparations, because ventricular muscle has a greater role in producing cardiac output than atrial muscle.

When 3 mg·kg^{-1} of propofol was administered intravenously to the support dog, the mean arterial pressure decreased by 33%, a blood-pressure drop equivalent to that observed during induction of anesthesia in humans [2,13]. Furthermore, an optimal dose of propofol for induction of anesthesia in dogs was reported to be

5 mg·kg^{-1} [14]. We chose a smaller dose (3 mg·kg^{-1}) because pentobarbital was administered beforehand as basal anesthesia. Therefore, it is reasonable to postulate that 3 mg·kg^{-1} i.v. propofol is clinically relevant, although we did not measure the blood concentrations of propofol. This dose of propofol induced decreases (10%–15%) in the contractile force of the ventricular preparation. This finding suggests that propofol mildly but significantly depresses the contractile force of the isolated ventricular myocardium at clinically relevant blood concentrations. This conclusion is in contrast to that of Mouren et al. [8]. However, Mouren et al. observed that propofol at a high concentration reduced dP/dt_{max} by 10% (but not significantly) in the blood-perfused rabbit heart, and it further decreased dP/dt_{max} by more than 50% in the buffer-perfused heart. Differences in the experimental design (including methods and animal species) may explain these discrepancies.

In the left ventricular preparation, we also confirmed that propofol decreases myocardial contractility, with thiopental as control, by injecting agents directly into the feeding artery of the preparation. However, no significant difference between the two dose-response curves was seen. This finding is different from our previous observation in isolated canine atria, in which the negative inotropic effects of propofol were greater than those produced by thiopental [12]. It is, however, difficult to find a small difference when the negative inotropic effects of propofol at the doses used in the ventricle were much less than those in the atrium. On the other hand, the optimal dose of thiopental for induction of anesthesia is generally accepted to be 1.6 to 2 times larger than that of propofol [2,15]. Therefore, we can conclude that the negative inotropic effect of propofol is less prominent than that of thiopental at anesthetic induction doses. This finding is in accordance with the reports of Park et al. [3] and Azari et al. [5].

In summary, our findings suggest that clinically relevant doses of propofol have direct depressant effects on myocardial contractile force, and its depressant actions are less prominent than those of thiopental at anesthetic induction doses.

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