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Negative inotropic action of propofol is enhanced in the acute ischemic myocardium of dogs

Takuji Maekawa, Sungsam Cho, Shunji Takahashi, Tetsuya Hara, Shiro Tomiyasu, Tetsuji Makita, and Koji Sumikawa

Department of Anesthesiology, Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan

Abstract
Purpose. We investigated the effects of propofol on contractility and oxygen balance in acute ischemic myocardium and compared them with those of normal myocardium using a coronary microembolization model in dogs.
Methods. In open-chest dogs, the left anterior descending coronary artery (LAD) was perfused through an extracorporeal bypass from the carotid artery. Regional myocardial contractility and myocardial oxygen balance were evaluated along with segment shortening (%SS), regional myocardial oxygen consumption (MVO_2), and lactate extraction ratio (LER) of the area perfused by the LAD. Acute ischemia was produced by repeated injection of microspheres into the LAD-perfused area until %SS decreased by 50% of baseline.
Results. In normal myocardium, intracoronary infusion of propofol at doses of 1.2 and 2.4 $mg \cdot kg^{-1} \cdot h^{-1}$ caused slight decreases in %SS to 83% ± 8% and 80% ± 10%, respectively. In ischemic myocardium, propofol caused greater decreases in %SS (59% ± 18% and 35% ± 20%, respectively). The changes in MVO_2 after propofol infusion generally paralleled the changes in %SS, but LER was not changed in either ischemic or normal myocardium.
Conclusion. Propofol causes a greater decrease in the contractility of acute ischemic myocardium as compared with normal myocardium in which myocardial oxygen imbalance is not involved as a mechanism.

Key words Propofol · Ischemia · Coronary microembolization · Myocardial contractility · Myocardial oxygen balance

Introduction

Propofol is used with increasing frequency for anesthetic management or postoperative sedation in high-risk patients with compromised myocardial function, as in conditions such as acute coronary syndrome (ACS). Therefore, it is important to evaluate the cardiovascular effects of propofol in this situation. Propofol has been reported to have no direct negative inotropic effect at therapeutic concentrations in normal myocardium [1–3]; however, the effect of propofol on contractility in chronic diseased myocardium is controversial [4–7]. Furthermore, there have been few reports concerning the effect of propofol on myocardial contractility in acute heart failure, such as that occurring in ACS. Mayer et al. reported that the myocardial depressant effect of propofol was more pronounced in acute ischemic myocardium than in normal myocardium, and suggested that the decrease in coronary perfusion pressure (CPP) and tachycardia worsen the function of ischemic myocardium [8].

This study was carried out to test the following hypotheses: (1) whether the negative inotropic effect of propofol, as a direct myocardial action, could be enhanced in acute ischemic myocardium as compared with normal myocardium and (2) whether propofol might have an adverse effect on regional myocardial oxygen balance in acute ischemic myocardium. We used the microembolization model in dogs as described previously [9]. In this study, an extracorporeal perfusion system, ventricular pacing at a constant rate, and intracoronary infusion of propofol were used to assess the direct effects of propofol on myocardial contraction, coronary blood flow (CBF), and myocardial oxygen consumption (MVO_2) under stable systemic hemodynamic conditions.

Materials and methods

Surgical preparations

All experimental procedures and protocols used in this investigation were reviewed and approved by the

Address correspondence to: T. Maekawa
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Institutional Animal Care Committee. Twenty-one mongrel dogs (11–18 kg) were anesthetized with intravenous injection of α-chloralose, 100 mg·kg^{-1}, followed by continuous infusion of α-chloralose (10 mg·kg^{-1}·h^{-1}) and fentanyl (5 μg·kg^{-1}·h^{-1}) throughout the study period. After tracheal intubation, mechanical ventilation with a Harvard respiratory pump (Harvard Apparatus, South Natick, MA, USA) was facilitated by an intermittent intravenous infusion of vecuronium, 0.2 mg·kg^{-1}. Tidal volume, respiratory rate, and inspired oxygen concentration were adjusted to maintain the arterial carbon dioxide tension (Pa_{CO_2}) at between 35 and 40 mmHg and the arterial oxygen tension (Pa_{O_2}) at between 100 and 300 mmHg. End-tidal CO_2 concentration was continuously monitored by using a gas analyzer (Capnomac Ultima; Datex, Helsinki, Finland). Lactate Ringer's solution was infused at a rate of 5 ml·kg^{-1}·h^{-1}. Sodium bicarbonate was administered to maintain the base deficit within 5 mEq·l^{-1}. Arterial blood glucose concentration was maintained at a baseline value with an intravenous infusion of 10% dextrose as needed throughout the study period. The esophageal temperature was maintained at between 36° and 37°C throughout the study period by using a warmer blanket and a heating lamp.

A heparin-filled catheter was inserted into the left femoral vein to infuse fluid and drugs. A thoracotomy was performed at the left fifth intercostal space. The pericardium was incised while the left lung was gently retracted. After the intravenous infusion of sodium heparin, 750 U·kg^{-1} bolus plus 250 U·kg^{-1}·h^{-1}, to prevent blood coagulation, the left anterior descending coronary artery (LAD) was cannulated with a 13- or 14-gauge thin-wall stainless-steel cannula and perfused with blood from the left carotid artery through an extracorporeal bypass tube. CPP was measured from the sidearm of the bypass using a pressure transducer-tipped catheter (PC500; Millar Instruments, Houston, TX, USA); the CBF of the area perfused by the LAD (rCBF) was measured with an ultrasonic flow probe (ADP17; Crystal Biotech, Hopkinton, MA, USA) attached at the bypass. A 24-gauge catheter was inserted into the epicardial vein near the center of the area perfused by the LAD to allow coronary venous blood sampling. A pressure transducer-tipped catheter (PC500; Millar Instruments) was inserted into left ventricular (LV) cavity through an incision in the apex for continuous recording of LV pressure (LVP). The peak rate of increase in LVP ($LVdP/dt_{max}$) was determined by electronic differentiation of the LVP waveform. A pair of ultrasonic segment length transducers was implanted in the subendocardium of the area perfused by the LAD to measure changes in regional contractile function (percentage segment shortening [%SS]). Segment length was monitored by ultrasonic amplifiers (VF-1; Crystal Biotech). End-systolic segment length (ESL) was determined 10 ms before maximum negative LVdP/dt, and end-diastolic segment length (EDL) was determined 10 ms before dP/dt first exceeded 140 mmHg·s^{-1} (immediately prior to the onset of LV isovolemic contraction). %SS was calculated using the formula: $\%SS = (EDL - ESL) \times 100 \times EDL^{-1}$. Heart rate influences some hemodynamic parameters, especially coronary hemodynamics. To avoid this problem, formalin was injected into the region of the atrioventricular (AV) node to produce a complete block of AV conduction, and the heart was paced via the right ventricle at 120 beats·min^{-1} throughout the study period. All hemodynamic data were continuously monitored on a polygraph and digitized via a computer interfaced with an analog-to-digital converter (HEM; Physio-Tech, Tokyo, Japan).

Chemical analysis

Heparinized blood samples were taken from the coronary artery and vein to determine pH, P_{CO_2}, P_{O_2}, hemoglobin concentration, oxygen saturation, and lactate concentration (ABL 620; Radiometer, Copenhagen, Denmark). Coronary arteriovenous blood oxygen difference (AVO_2D) was assessed by the difference between coronary arterial and venous oxygen levels. MVO_2 (ml·min^{-1}) was calculated as rCBF (ml·min^{-1}) × AVO_2D (ml·dl^{-1}). The lactate extraction ratio (LER) was obtained by the coronary arteriovenous difference in lactate concentration multiplied by 100 and divided by the arterial lactate concentration.

Experimental protocol

The experimental protocol is shown in Fig. 1. After surgical preparation and a stabilization period, baseline %SS and hemodynamic data were collected and coronary arterial and venous blood were sampled simultaneously. The dogs were randomly allocated to one of three groups. Group I ($n = 7$) had ischemic myocardium and received saline; group IP ($n = 7$) had ischemic myocardium and received propofol; group NP ($n = 7$) had normal myocardium and received propofol. Plastic microspheres (NEN-TRAC microspheres, Life Science Products, Boston, MA, USA), 50 μm in diameter, were dispersed in 10% dextran containing Tween 80 to a concentration of 1 mg·ml^{-1}. In the I and IP groups, coronary microembolization was produced by repeated injection of 0.5–1.0 ml of the microsphere suspension into the area perfused by the LAD via a site distal to the bypass. The injections were made every 5 min until %SS of the perfused area decreased to 50% of baseline.

Thirty minutes after completion of coronary microembolization, the next measurement was done

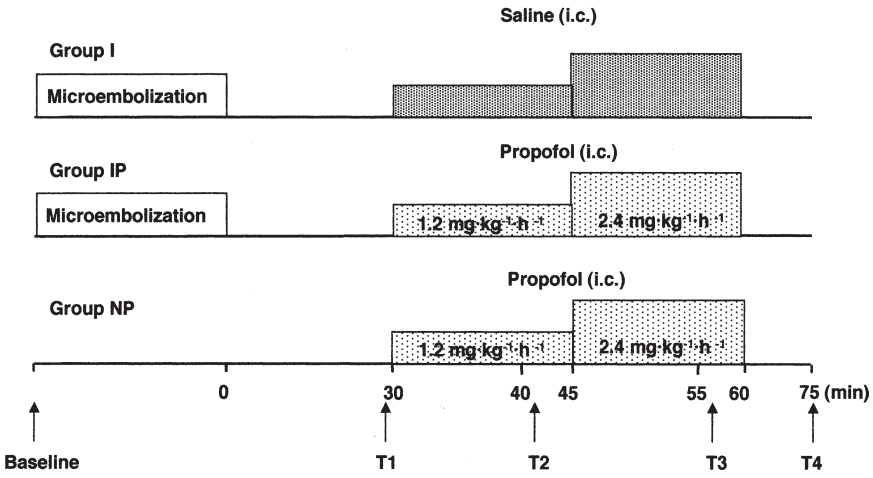

Fig. 1. Experimental protocol. *Group I* had ischemic myocardium and received saline; *group IP* had ischemic myocardium and received propofol; *group NP* had normal myocardium and received propofol. *T1*, before infusion of propofol or saline; *T2*, 10 min after starting infusion of 1.2 mg·kg^{-1}·h^{-1} of propofol or the same infusion rate of saline; *T3*, 10 min after starting infusion of 2.4 mg·kg^{-1}·h^{-1} of propofol or the same infusion rate of saline; *T4*, 15 min after discontinuing propofol or saline; *i.c.*, intracoronary infusion

(T1). Then, dogs in group IP were treated with two consecutive infusions of propofol (1.2 and 2.4 mg·kg^{-1}·h^{-1}) into the coronary artery with a syringe pump at a site distal to the LAD bypass for 15 min, and the measurements were done 10 min after starting the infusion of each dose of propofol (T2, 3). The final measurement was done 15 min after discontinuation of test substance administration (T4). The dogs in group I received saline at the same infusion rate as propofol, resulting in a range of infusion rates of 0.02–0.07 ml·min^{-1}. The dogs in group NP received propofol following the same time course as for group IP. The coronary blood concentration of propofol was calculated by dividing the intracoronary infusion rate (μg·min^{-1}) by rCBF (ml·min^{-1}). These doses and the steady-state infusion time of propofol were set on the basis of a previous study that showed a slight but significant decrease in %SS [1], and these concentrations of propofol corresponded to 5 and 10 times the clinical plasma concentrations for anesthetic management.

Statistical analyses

All data were expressed as mean ± SD. Data within a group and baseline data among groups were analyzed with analysis of variance followed by Fisher's protected least significant difference (PLSD) test. The percentage change in %SS and the calculated coronary blood concentrations of propofol in groups IP and NP were compared using the two-tailed unpaired *t* test. Statistical significance was defined as $P < 0.05$.

Results

There were no significant differences in any measurement at baseline among groups. LVSP, LVEDP, LVdP/dt_{max}, and CPP remained unchanged during the whole study period in all groups (Tables 1 and 2). Coronary microembolization decreased %SS, MVO_2, and LER in groups I and IP (Table 2).

Propofol significantly increased rCBF in group NP but not in group IP. Propofol caused a significant decrease in %SS and MVO_2 in group IP but not in group NP (Table 2). %SS at 1.2 and 2.4 mg·kg^{-1}·h^{-1} of propofol in group IP, 59% ± 18% and 35% ± 20% of prepropofol value, were significantly lower than those in group NP, 83% ± 8% and 80% ± 10%, respectively. %SS depression at 2.4 mg·kg^{-1}·h^{-1} of propofol was greater than that at 1.2 mg·kg^{-1}·h^{-1} of propofol in ischemic but not in normal myocardium (Fig. 2). LER remained unchanged after propofol administration, suggesting that decreased MVO_2 in both ischemic groups was a result of the decrease in %SS. There was no significant difference in the calculated coronary blood concentrations of propofol between groups IP and NP. %SS, MVO_2, and rCBF after discontinuing propofol recovered toward the prepropofol values (Table 2).

Discussion

The present results show that propofol decreases the %SS of ischemic myocardium more than that of normal myocardium, and decreases MVO_2 with no change in LER. The results indicate that the myocardial depressant effect of propofol is significantly enhanced in acute ischemic myocardium as compared with normal myocardium, and that propofol has no adverse effect on the regional myocardial oxygen balance. Coronary microembolization decreased %SS, MVO_2, and LER, whereas rCBF remained unchanged in this study. Coronary microembolization results in perfusion–contraction mismatch, i.e., myocardial function is

Table 1. Systemic hemodynamics

	Baseline	T1	T2	T3	T4
HR (beats·min^{-1})	120	120	120	120	120
LVSP (mmHg)					
Group I	109 ± 17	104 ± 15	108 ± 13	108 ± 15	106 ± 13
Group IP	102 ± 9	105 ± 10	104 ± 12	103 ± 12	109 ± 13
Group NP	109 ± 9	110 ± 10	108 ± 12	108 ± 12	109 ± 15
LVEDP (mmHg)					
Group I	7 ± 1	7 ± 2	7 ± 2	8 ± 2	8 ± 2
Group IP	5 ± 3	6 ± 2	7 ± 4	7 ± 4	7 ± 4
Group NP	5 ± 1	4 ± 1	5 ± 2	5 ± 2	4 ± 2
LVdP/dt$_{max}$ (mmHg·s^{-1})					
Group I	2349 ± 648	2125 ± 561	2272 ± 546	2172 ± 604	2264 ± 630
Group IP	2281 ± 405	2163 ± 384	2110 ± 320	2125 ± 395	2195 ± 347
Group NP	2566 ± 426	2562 ± 361	2519 ± 363	2411 ± 387	2473 ± 430

Values are mean ± SD (n = 7 for each group)
Group I had ischemic myocardium and received saline; group IP had ischemic myocardium and received propofol; group NP had normal myocardium and received propofol
T1, before infusion of propofol or saline; T2, 10 min after starting infusion of 1.2 mg·kg^{-1}·h^{-1} propofol or the same infusion rate of saline; T3, 10 min after starting infusion of 2.4 mg·kg^{-1}·h^{-1} propofol or the same infusion rate of saline; T4, 15 min after discontinuing propofol or saline. HR, heart rate; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; LV dP/dt$_{max}$, maximum rate of increase in left ventricular pressure

Table 2. Regional coronary hemodynamics, percent segment shortening, regional myocardial oxygen balance, and calculated coronary blood concentration of propofol

	Baseline	T1	T2	T3	T4
CPP (mmHg)					
Group I	94 ± 11	92 ± 9	93 ± 10	94 ± 10	92 ± 10
Group IP	94 ± 7	97 ± 8	96 ± 10	93 ± 8	94 ± 10
Group NP	98 ± 10	98 ± 11	98 ± 12	98 ± 11	97 ± 10
rCBF (ml·min^{-1})					
Group I	10.2 ± 1.2	12.1 ± 2.8	11.5 ± 3.1	12.4 ± 4.1	12.3 ± 3.7
Group IP	10.3 ± 4.5	12.3 ± 4.3	11.5 ± 3.7	11.2 ± 3.6	12.8 ± 5.0
Group NP	8.9 ± 2.3	9.3 ± 1.9	10.0 ± 2.1	11.7 ± 2.6*	10.5 ± 2.5
%SS (%)					
Group I	19 ± 4	10 ± 2*	10 ± 2*	10 ± 2*	10 ± 2*
Group IP	17 ± 6	9 ± 4*	6 ± 3*	3 ± 3*¶	6 ± 2*
Group NP	17 ± 4	16 ± 5	14 ± 4	13 ± 4	16 ± 4
MVO_2 (ml·min^{-1})					
Group I	1.04 ± 0.46	0.66 ± 0.28*	0.57 ± 0.25*	0.55 ± 0.26*	0.55 ± 0.25*
Group IP	0.91 ± 0.30	0.56 ± 0.16*	0.56 ± 0.21*	0.34 ± 0.07*¶‡	0.56 ± 0.07*
Group NP	0.85 ± 0.24	0.83 ± 0.24	0.71 ± 0.25	0.67 ± 0.17	0.85 ± 0.31
LER (%)					
Group I	29 ± 12	−3 ± 13*	1 ± 10*	3 ± 9*	6 ± 4*
Group IP	27 ± 15	−2 ± 6*	1 ± 6*	1 ± 6*	4 ± 8*
Group NP	29 ± 12	27 ± 11	23 ± 16	22 ± 8	21 ± 14
CCBCP (μg·ml^{-1})					
Group IP			25.4 ± 5.6	53.2 ± 12.9‡	
Group NP			28.6 ± 5.3	50.1 ± 13.5‡	

Values are mean ± SD (n = 7 for each group)
CPP, coronary perfusion pressure; rCBF, regional coronary blood flow; %SS, percent segment shortening; MVO_2, regional myocardial oxygen consumption; LER, lactate extraction ratio; CCBCP, calculated coronary blood concentration of propofol
* $P < 0.05$ versus baseline, ¶ $P < 0.05$ versus T1, ‡ $P < 0.05$ versus T2

markedly reduced, whereas CBF remains unchanged or even increases. Moreover, the microembolization decreased LER, indicating induction of myocardial ischemia. These results were in accordance with those of Kitakaze and Dörge [9,10].

Mayer et al. showed that the myocardial depressant effect of propofol, 5 mg·kg^{-1} as an intravenous bolus, was more pronounced in ischemic myocardium than in normal myocardium in chronically instrumented dogs and suggested that the decrease in CPP and tachycardia

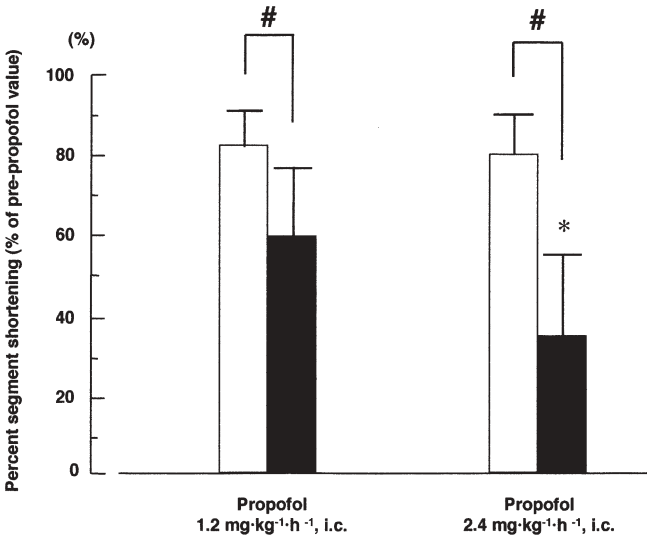

Fig. 2. Changes in myocardial contractility during intracoronary infusion of propofol in normal (*white bar*) and ischemic myocardium (*black bar*). *Error bars* show SD from the mean ($n = 7$ for each group). #$P < 0.05$ between normal and ischemic myocardium, *$P < 0.05$ versus $1.2\,mg{\cdot}kg^{-1}{\cdot}h^{-1}$ of propofol

after propofol administration could worsen the function of ischemic myocardium [8]. However, our results show that propofol decreases %SS of ischemic myocardium more than that of normal myocardium under stable systemic hemodynamic conditions. Thus propofol's depressant action was not the result of changes in systemic hemodynamic conditions. The discrepancy between our results and those of Mayer et al. might be caused by the different propofol concentrations employed. Otherwise stated, only very high doses of propofol might enhance the myocardial depressant effect in acute ischemic myocardium as compared with normal myocardium. We used saline as a control, but use of intralipid emulsion of propofol has been reported and had no effect or only small inhibitory effects on myocardial contractility at higher concentrations than that used in our study [5,11], so it is unlikely that the depression of systolic function could have been caused by the emulsion.

Belo et al. reported that intracoronary administration of propofol, 5 or $20\,\mu g{\cdot}ml^{-1}$, did not affect either myocardial contractility or the myocardial oxygen balance [2]. In the present study, propofol caused a decrease in myocardial contractility probably because our blood concentrations of propofol were higher than those of Belo et al. However, even at high blood concentrations, propofol did not affect the myocardial oxygen balance in either normal or ischemic myocardium. The results suggest that propofol would not cause further ischemia in the acute ischemic myocardium. The mechanisms of the different sensitivities to the myocardial depressant effect of propofol between normal and ischemic myocardium are unclear from our study, but it is clear, at least, that an oxygen imbalance is not involved in the mechanism. Propofol would modify some mechanisms of contractility in acute ischemic myocardium. Given this explanation, several mechanisms are possible. First, in the failing myocardium, abnormalities in L-type Ca^{2+} channel density or regulation may have profound effects on cardiac function [12,13]. Propofol may also have an inhibitory effect on the L-type Ca^{2+} channel, which is in part involved in the mechanism of myocardial depression [14]. Therefore, it is possible that L-type Ca^{2+} channel inhibition seen in failing myocardium might be further compounded by adding propofol. Second, propofol might increase myofilament Ca^{2+} sensitivity, which might offset propofol-induced reduction in intracellular Ca^{2+} concentration [5,11]. However, in the failing myocardium, myofilament Ca^{2+} sensitivity may decrease [15]. So, it is possible that myofilament Ca^{2+} sensitization by propofol might be blunted in the ischemic myocardium. Third, Zhou et al. reported that $200\,\mu M$ of propofol depressed cardiac function in part via antagonisms to β-adrenoreceptor binding of catecholamines and subsequent receptor activation [16]. It is also possible that sympathetic activation, as a compensatory mechanism of pump failure seen in acute ischemic myocardium [17], is attenuated by adding propofol.

Propofol at a high blood concentration would cause direct dilation of coronary resistance vessels [1]. In group NP, at the higher dose of propofol, rCBF increased significantly despite MVO_2 being unchanged, indicating that propofol has a direct coronary vasodilatory effect in the normal heart. In contrast, propofol did not affect rCBF in group IP. Microembolized myocardium is a mixture of hypoperfused myocardium and surrounding hyperperfused myocardium with vasodilation secondary to a release of adenosine [18]. Therefore, the direct coronary vasodilatory effect of propofol would be blunted in the ischemic myocardium.

Coetzee et al. reported that after discontinuing propofol infusion, recovery of myocardial contractility was delayed [19]. In contrast, in our study, %SS in both groups recovered to near prepropofol values 15 min after discontinuing propofol infusions. We assume that this contradiction was caused by the duration of propofol infusion and the intravenous, rather than intracoronary, administration of propofol. Our results are consistent with those of Ismail et al., who used similar conditions to ours [1].

There are several limitations to this study. First is the use of supraclinical concentrations of propofol, thus

making it difficult to apply the results to clinical situations. Further investigation is needed to determine whether propofol is suitable for sedation and anesthesia for patients with acute myocardial ischemia. Second, species differences may exist in the myocardial effects of propofol and the characteristics of coronary circulation. Some reports demonstrated that the effect of propofol on diseased myocardium was not modified in cardiomyopathic hamsters [6], in hypertrophic rabbit heart [4], or in human myocardium isolated from patients with congestive heart failure [5]. In contrast, Hebbar et al. reported that porcine myocytes in congestive heart failure were more sensitive than normal myocytes to the negative inotropic effect of propofol [7]. Our results and those of Mayer et al. show that the myocardial depressant effect of propofol is more pronounced in ischemic myocardium using acute ischemic heart in a dog model. Thus, the discrepancy in the effects of propofol on the contractility of diseased myocardium might result from differences among species. Third, we used α-chloralose for basal anesthesia, so some modification by α-chloralose of the effects of propofol might have caused the differences between our study and some of the studies that do not agree with our findings. However, α-chloralose provides a steady-state light level of anesthesia with a stable baseline in cardiovascular variables, and is useful for investigating the direct effects of propofol on the cardiovascular system [20]. Fourth, we assessed segmental LV function during the absence of atrial contraction because of pacing, so it may be difficult to apply our results to global cardiac function.

In conclusion, supraclinical concentrations of propofol caused a greater decrease in the contractility of acute ischemic myocardium as compared with normal myocardium in dogs. MVO_2 changes paralleled those of %SS, and LER was not changed, indicating that oxygen imbalance was not involved in the mechanism of propofol's depressant action.

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