Acta Med. Okayama, 2012
Vol. 66, No. 6, pp. 435–442

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Original Article

Effects of Propofol on Left Ventricular Mechanoenergetics in the Excised Cross-circulated Canine Heart

Waso Fujinaka[a,b], Juichiro Shimizu[a], Gentaro Iribe[a], Takeshi Imaoka[a], Yu Oshima[a], Takahiko Kiyooka[a], Kiyoshi Morita[b], and Satoshi Mohri[a,c]*

Departments of [a]Cardiovascular Physiology and [b]Anesthesiology and Resuscitology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700–8558, Japan, and [c]Department of Physiology 1, Kawasaki Medical School, Kurashiki, Okayama 701–0192, Japan

Although propofol is commonly used for general anesthesia, its direct effects on left ventricular (LV) contractility and energetics remain unknown. Accordingly, we studied the effects of intracoronary propofol on excised cross-circulated canine hearts using the framework of the Emax (a contractility index)-PVA (systolic pressure-volume area, a measure of total mechanical energy)-Vo_2 (myocardial oxygen consumption per beat) relationship. We obtained 1) the Vo_2-PVA relationship of isovolumic contractions with varied LV volumes at a constant Emax, 2) the Vo_2-PVA relationship with varied LV volumes at a constant intracoronary concentration of propofol, and 3) the Vo_2-PVA relationship under increased intracoronary concentrations of either propofol or $CaCl_2$ at a constant LV volume to assess the cardiac mechanoenergetic effects of propofol. We found that propofol decreased Emax dose-dependently. The slope of the linear Vo_2-PVA relationship (oxygen cost of PVA) remained unchanged by propofol. The PVA-independent Vo_2-Emax relationship (oxygen cost of Emax) was the same for propofol and Ca^{2+}. In conclusion, propofol showed a direct negative inotropic effect on LV. At its clinical concentrations, decreases in contractility by propofol were relatively small. Propofol shows mechanoenergetic effects on the LV that are similar to those of Ca^{2+} blockers or ß-antagonists—*i.e.*, it exerts negative inotropic effects without changing the oxygen costs of Emax and PVA.

Key words: anesthesia, heart, contractility, myocardial oxygen consumption

Propofol has been reported to have multiple actions on the myocardium by inhibiting L-type Ca^{2+} channels [1], sarcoplasmic reticulum (SR) Ca^{2+} handling [2], and K^+ channels [3], and increasing Ca^{2+} sensitivity [4]. The combination of these negative and positive inotropic mechanisms of propofol has the potential to result in complex outcomes of cardiac contractility. While earlier studies using open chest canine hearts tried to determine the direct effect of propofol on the pump function of the left ventricle (LV), it remains unclear whether propofol has a negative inotropic effect on beating hearts because simultaneous hemodynamic changes or neural regulation can affect cardiac contractility [5–7]. To resolve this issue, a rigorous analysis of LV contractility without concomitant changes in preload, afterload and baroreflex activity is needed to elucidate the inotropism of propofol. Moreover, although an effect of propofol on myocardial oxygen consumption has been reported in several studies [6–8], the energetic effects of propofol on a beating whole heart remain unknown.

The purpose of this study was to analyze the over-

Received March 14, 2012; accepted May 10, 2012.
*Corresponding author. Phone:+81–86–462–1111; Fax:+81–86–462–1199
E-mail:smohri@med.kawasaki-m.ac.jp (S. Mohri)

all effects of propofol on cardiac mechanoenergetics in the excised (denervated) cross-circulated (blood-perfused) canine heart. To evaluate the cardiac inotropic effect of propofol, we used the most reliable contractility index, Emax, which is practically independent of ventricular loading conditions [9, 10]. To assess the effects of propofol on cardiac energetics, we used the relationship between Vo_2 (myocardial oxygen consumption per beat) and PVA (systolic pressure-volume area: a measure of total mechanical energy) of the LV [9].

Materials and Methods

All procedures in this study were approved by the Okayama University Institutional Review Board.

Surgical preparation. We performed the experiments on the excised, cross-circulated canine heart preparation (Fig. 1) [11, 12]. The left atrium of the excised heart was opened and a latex balloon mounted on a rigid connector was fitted into the LV. LV pressure was measured with a pressure gauge (model P-7; Konigsberg Instruments, Pasadena, CA, USA) placed inside the apical end of the balloon. The water-filled balloon was connected to a custom-made volume servopump (Air-Brown, Tokyo, Japan) that controlled the LV volume.

The heart was paced at 129 ± 11 (beats/min), ~20% above the spontaneous heart rate at ~37.0℃. We adopted the isovolumic contraction mode because the Vo_2-PVA relation is largely independent of the contraction mode [9].

Oxygen consumption. Total coronary blood flow (CF) was measured with an electromagnetic flowmeter (MFV-3200; Nihon Kohden, Tokyo, Japan). The coronary arteriovenous O_2 content difference (AVO_2D) was measured with an in-line oximeter (PWA-200S; Shoe Technica Inc., Chiba, Japan). The Vo_2 was obtained as $CF \times AVO_2D$/heart rate [11, 12].

Emax and PVA. LV contractility Emax was determined as the maximum ratio of $P(t)/[V(t)-V_0]$ [10], where V_0 was the volume at which peak isovolumic pressure was zero. PVA was calculated as the area in the P-V diagram as schematically shown in Fig. 2A. Emax and PVA were normalized for 100 gLV.

Experimental protocol. The experiments consisted of 4 runs in each of 5 hearts:

1. Control volume run: We obtained the volume loaded Vo_2-PVA relationship (Fig. 2B) of steady-state isovolumic contractions produced at 4–10 different LV volumes (6–24 ml).

2. Propofol volume run: Under coronary infusion

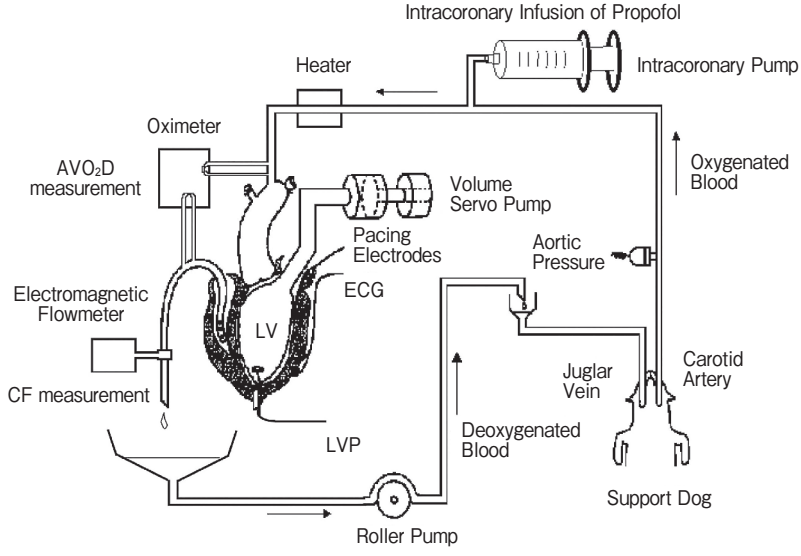

Fig. 1 Schematic illustration of the canine cross-circulated heart preparation. LV, left ventricle; LVP, LV pressure; ECG, electrocardiogram; AVO_2D, arteriovenous O_2 content difference; CF, coronary flow.

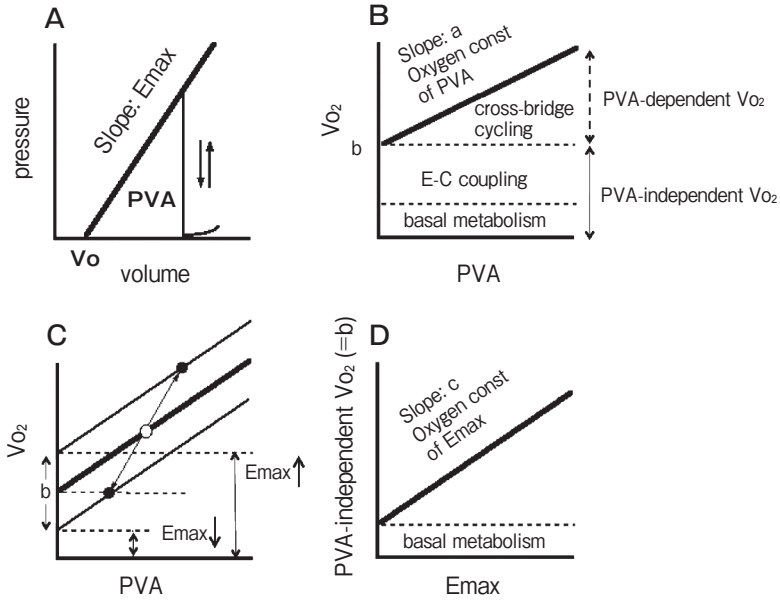

Fig. 2 Schematic illustration of the framework of the relation among left ventricular Emax (a contractility index), PVA (systolic pressure-volume area: a measure of total mechanical energy), and Vo_2 (myocardial O_2 consumption per beat) used in the present study. Emax, the slope of the end-systolic pressure-volume relation, sensitively reflects ventricular contractility (Panel A). PVA correlates linearly with Vo_2 in a load-independent manner in a stable contractile state (Panel B). The slope (*a*) of the Vo_2-PVA relation at a constant Emax represents the O_2 cost of PVA. Vo_2 can be divided at the Vo_2 intercept (*b*) of the Vo_2-PVA relation into the PVA-independent and the PVA-dependent Vo_2 components (Panel B). The PVA-dependent Vo_2 is related to cross-bridge cycling. The PVA-independent Vo_2 is related to the total Ca^{2+} handling in the excitation-contraction coupling and basal metabolism. Panel C indicates that the Vo_2-PVA data point deviates from a data point of the control Vo_2-PVA relation with changes in Emax by an inotropic intervention at a constant LV volume. This steeper relation (composite Vo_2-PVA relation) traversed multiple volume-loaded Vo_2-PVA relations for different contractility (Emax) levels. In this relation, the PVA-independent Vo_2 increases or decreases in proportion to an increase or a decrease in Emax, respectively. The slope (*c*) of the relation between the PVA-independent Vo_2 and Emax represents the O_2 cost of Emax, and the y intercept (*d*) of this relation indicates the PVA-independent Vo_2 at zero Emax, which is nearly equal to the basal metabolism (Panel D).

of propofol that decreased Emax to ~70% of the control level, we obtained another Vo_2-PVA relation (Fig. 2C) by varying the LV volume. The propofol concentration was measured by high-performance liquid chromatography.

3. Propofol and calcium inotropism runs: We performed a propofol inotropism run to obtain a different type of Vo_2-PVA relationships at a single, fixed LV volume. Propofol was infused intracoronarily to vary Emax, Vo_2, and PVA, and then we obtained the Vo_2-PVA relationship (Fig. 2C). We depressed Emax to approximately half the control level by increasing the propofol concentration in steps to 60 μg/ml.

We next infused $CaCl_2$ (1%) in steps to increase Emax to approximately double the control value. We used calcium rather than catecholamine because calcium does not affect the complex phosphorylation processes of contractile proteins [13].

Data analyses

1. Vo_2-PVA relations: Vo_2 and PVA data in volume runs were subjected to linear regression analysis (Fig. 2B): $Vo_2 = a \cdot PVA + b$, where a is the slope of the regression line and b is the Vo_2 intercept. $a \cdot PVA$ represents PVA-dependent Vo_2 and b represents PVA-independent Vo_2. The coefficient a was the oxygen cost of PVA [10].

Vo_2 and PVA data in each inotropism run were also subjected to linear regression analysis to obtain a composite Vo_2-PVA relation (Fig. 2C).

2. PVA-independent Vo_2: The PVA-independent Vo_2 for each Emax level during either the propofol or calcium run was calculated as the Vo_2 minus PVA-dependent Vo_2 for the respective PVA. This PVA-dependent Vo_2 was calculated as the product of the same slope value a and the PVA of this contraction. The PVA-independent Vo_2 at each Emax level was

calculated as LV Vo_2 minus a・PVA.

3. Oxygen cost of Emax: The relation between PVA-independent Vo_2 values and the corresponding Emax values in either the propofol or calcium inotropism run was obtained by regression analysis in each heart (Fig. 2D). The slope c of the regression line was identified as the oxygen cost of Emax [10]. We used calcium rather than a catecholamine as a positive inotropic agent because calcium administration increases cardiac contractility without primarily involving the phosphorylation processes of contractile proteins [14].

Preliminary experiment. To confirm the effect of propofol on the LV basal metabolism, we performed KCl-arrest runs in the control and under propofol infusion ($n = 3$, $60\,\mu g/ml$). The heart was arrested at V_0 by a continuous infusion of 0.3 mol/l KCl solution at 1–2.5 ml/min into the coronary artery. When CF and AVO_2D reached a steady state during KCl arrest, Vo_2 was measured as basal metabolic Vo_2. PVA-independent Vo_2 consists of oxygen consumption for excitation-contraction (E–C) coupling and basal metabolism (Fig. 2B). Propofol did not affect basal metabolic Vo_2 (0.92 ± 0.63 in the control and 0.91 ± 0.71 ml $O_2 \cdot min^{-1} \cdot 100g^{-1}$ in propofol infusion).

Statistical analysis. The Vo_2-PVA regression lines were compared between propofol and calcium inotropism runs and between control and propofol volume runs in each heart by the analysis of covariance (ANCOVA). The significance of the differences in their slopes and elevations was tested by the F test. ANCOVA was also used to compare the regression lines of PVA-independent Vo_2 on Emax between the propofol and calcium inotropism runs. Comparison of paired mean values was performed by Student's paired t-test. A value of $p < 0.05$ was considered statistically significant. All data are expressed as the mean ± SD.

Results

Control and propofol volume runs. Fig. 3A shows the Vo_2-PVA relations obtained in control and propofol volume runs in a heart. There were no significant differences in the slopes between the two Vo_2-PVA relations in any of the 5 hearts: the values were $(1.75 \pm 0.36) \times 10^{-5}$ in the control and $(1.73 \pm 0.32) \times 10^{-5}$ ml $O_2 \cdot mmHg^{-1} \cdot ml^{-1}$ in the propofol volume run, indicating that propofol did not affect the oxygen cost of PVA. Propofol significantly decreased the Vo_2 intercept value (0.0202 ± 0.0029 in the control to 0.0152 ± 0.0044 ml $O_2 \cdot beat^{-1} \cdot 100g^{-1}$ in the propofol volume run).

Composite Vo_2-PVA relations of calcium and propofol inotropism runs. Fig. 3B shows the Vo_2-PVA relationships in the control volume run and the calcium and propofol inotropism runs. The Vo_2-PVA data points descended more sharply when Emax

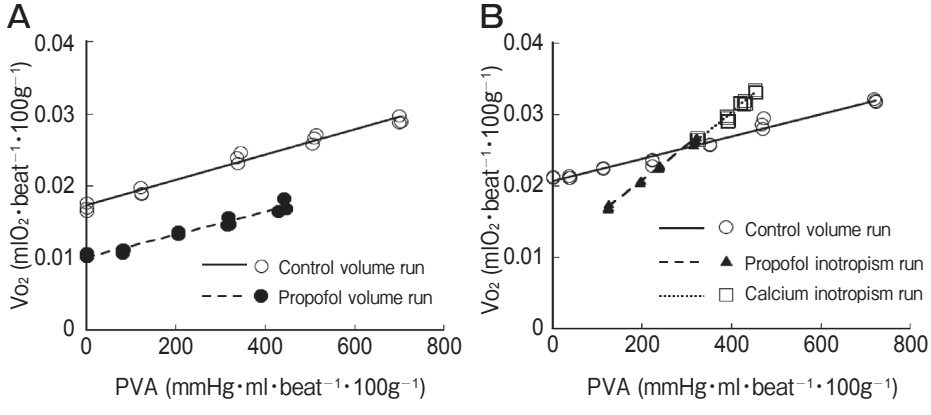

Fig. 3 (Panel A) Vo_2-PVA relationships in the control volume run (open circles; $Vo_2 = 1.76 \times 10^{-5}$ PVA + 0.017, $r = 0.98$) and the propofol volume run (closed circles; $Vo_2 = 1.59 \times 10^{-5}$ PVA + 0.01, $r = 0.964$). Propofol shifted the volume-loaded Vo_2-PVA relation downward in a parallel manner. (Panel B) Vo_2-PVA relationships in the control volume run (open circles; $Vo_2 = 1.25 \times 10^{-5}$ PVA + 0.022, $r = 0.98$), the propofol inotropism run (closed triangles; $Vo_2 = 4.43 \times 10^{-5}$ PVA + 0.012, $r = 0.987$) and the calcium inotropism run (open squares; $Vo_2 = 4.89 \times 10^{-5}$ PVA + 0.011, $r = 0.969$). The Vo_2-PVA composite relations during the propofol inotropism run and calcium inotropism run (dashed and dotted lines) were steeper than the control volume loaded Vo_2-PVA relationships (solid line). The composite relations in the propofol and calcium inotropism runs are virtually superimposable (ANCOVA).

was decreased by propofol and ascended more steeply when Emax was increased by calcium than the volume loaded Vo_2-PVA relationship. The data points in the two inotropism runs moved in opposite directions, but their linear relationships were superimposable. The other four hearts also showed similar results.

Oxygen cost of Emax and dose-dependency of negative inotropism. Fig. 4A plots PVA-independent Vo_2 values against Emax values during the propofol and calcium inotropism runs in one heart. Here, PVA-independent Vo_2 decreased linearly when Emax was decreased by propofol and increased linearly when Emax was increased by calcium. No significant difference was found in either the slope or elevation between these two PVA-independent Vo_2-Emax relationships. The other four hearts showed similar results, *i.e.*, the same oxygen cost of Emax between propofol and calcium.

The representative patterns of Emax versus the intracoronary propofol concentrations are plotted as a percent of the control (no propofol infusion) in Fig. 4B. The fitting line was drawn by linear regression analysis. This figure shows the dose dependency of the negative inotropic effect of propofol. The mean value of the slopes was $-1.71 \pm 0.88\,\mu g^{-1}\cdot ml$.

Effects of propofol on LV contractility and other parameters. Table 1 compares Emax, PVA, Vo_2, and other cardio-hemodynamic parameters obtained at an identical intermediate LV volume between the control and propofol volume runs in 5 hearts. Propofol significantly decreased LVP, Emax, PVA, Vo_2, and AVO_2D but did not significantly affect CF at a constant LV volume.

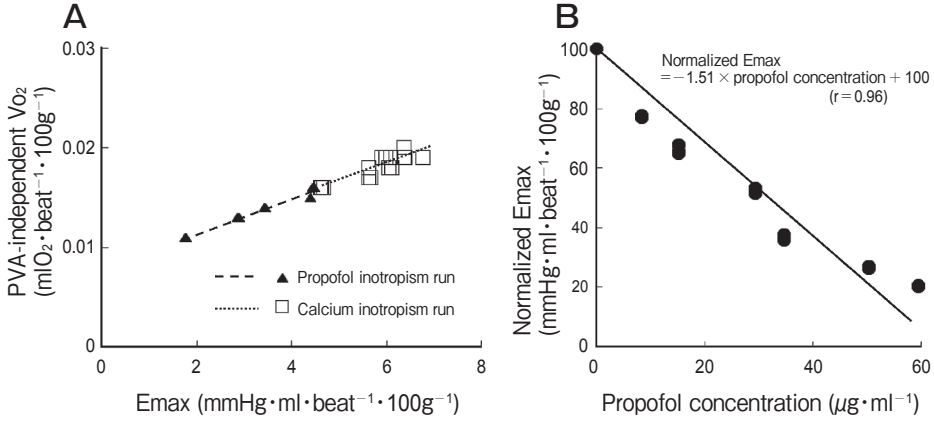

Fig. 4 PVA-independent Vo_2-Emax relationships in the propofol inotropism run (closed triangles; PVA-independent $Vo_2 = 2.0 \times 10^{-3}$ Emax + 0.008, r = 0.964) and the calcium inotropism run (open squares; PVA-independent $Vo_2 = 2.0 \times 10^{-3}$ Emax + 0.007, r = 0.916) (Panel A). Linear regression lines for the propofol inotropism run and calcium inotropism run are virtually superimposable (ANCOVA). The slope of the lines indicates the oxygen cost of Emax. The representative patterns of Emax versus blood propofol concentration in the propofol inotropism run are also shown (Panel B). The regression line indicates the direct negative inotropism of propofol.

Table 1 Effect of propofol on left ventricular mechanoenergetics and coronary circulation in propofol volume run

	LVP	Emax	PVA	Vo_2	CF	AVO_2D
Control	91.6 ± 21.6	8.4 ± 2.8	645 ± 111	0.042 ± 0.013	53 ± 14	6.2 ± 1.3
Propofol	64.8 ± 15.7*	5.9 ± 2.0*	451 ± 78*	0.029 ± 0.010*	48 ± 13	5.0 ± 1.2*

Each value (mean ± SD, n = 5) was compared between control volume run and the propofol volume run at intracoronary blood propofol concentration ($14.2 \pm 5.6\,\mu g\cdot ml^{-1}$) at a constant left ventricular (LV) volume ($18.8 \pm 3.1\,ml\cdot 100g^{-1}$) by Student's paired *t* test. *statistically significant at $p < 0.05$. LVP, LV pressure (mmHg); Emax, a contractility index ($mmHg\cdot ml^{-1}\cdot 100g^{-1}$); PVA, systolic pressure-volume area, a measure of total mechanical energy ($mmHg\cdot ml\cdot beat^{-1}\cdot 100g^{-1}$); Vo_2, oxygen consumption per beat ($ml\ O_2\cdot beat^{-1}\cdot 100g^{-1}$); CF, coronary flow ($ml\cdot min^{-1}\cdot 100g^{-1}$); AVO_2D, coronary arteriovenous oxygen content difference (vol%).

Discussion

We investigated the direct effect of intracoronary propofol on the LV mechanoenergetics using the framework of the Emax-PVA-Vo_2 relationship. The results indicated that propofol exerted a dose-dependent negative inotropic effect without affecting the oxygen cost of contractility. Although the intact *in situ* whole heart preparation [7, 8] is meaningful to assess the clinical relevance, many complicating factors, *e.g.*, the changes in various ventricular loading conditions and neural reflexes, would inevitably affect the experimental results. Therefore, the results obtained by experiments using blood-perfused, normothermic, and denervated whole canine hearts are essential to evaluate the direct effects of propofol on the LV contractility and mechanoenergetics.

Effect of propofol on LV contractility. The present results showed that propofol decreased Emax in a dose-dependent manner. Emax is virtually independent of ventricular loading conditions, unlike all other conventional myocardial contractility indices, including dP/dt max or Vmax [9].

In clinical use, the required blood propofol concentrations for major and non-major surgery have been reported to be $4.05 \pm 1.01\,\mu g$/ml and $2.97 \pm 1.07\,\mu g$/ml, respectively [15]. When these average values are substituted into the regression line in Fig. 4B, it can be seen that Emax decreases by only by 6.1% for major surgery and 4.5% for non-major surgery. Therefore, the negative inotropism of propofol is relatively small within clinical concentrations.

Oxygen cost of PVA. Propofol did not affect the oxygen cost of PVA and showed almost the same energetic effects on the oxygen cost of Emax as calcium, though in an opposite direction. Previous studies have reported that the oxygen cost of PVA remained unchanged even during negative and positive inotropic interventions with propranorol [16], calcium [17], catecholamines [17], fentanyl [11], and isoflurane [12], in normal canine hearts. In contrast, diseased heart models such as the hyperthyroid rabbit heart [18] and postischemic stunned canine heart [19] have shown increased oxygen costs of Emax due to the reduced Ca^{2+} sensitivity and the induced futile Ca^{2+} cycling via the SR. Propofol did not show oxygen-consuming effects like those seen in diseased hearts. Therefore, propofol preserved the overall myocardial efficiency of energy use from oxygen to total mechanical energy via ATP.

Oxygen cost of Emax. Propofol did not affect the basal metabolism in the KCl-arrest run. Therefore, the decreased PVA-independent Vo_2 by propofol would be mainly due to a decrease in the required energy for the E–C coupling.

This E–C coupling energy is critically affected by the fraction of Ca^{2+} handled (*i.e.*, released and removed) via the SR—*i.e.*, the intracellular Ca^{2+} recirculation fraction (RF)—because the internal (via the SR) Ca^{2+} handling has a $2Ca^{2+}$: ATP stoichiometry twice more efficient than the Ca^{2+}: ATP stoichiometry of external (transsarcolemmal) Ca^{2+} handling [20]. The fraction of calcium handled via the sarcoplasmic reticulum is controlled by the regulation of membrane proteins that induce influx and efflux of calcium—*i.e.*, the L-type calcium channel and sodium-calcium exchanger (NCX), which cause cardiac contraction and relaxation. It has been reported that propofol showed positive inotropism via the reverse mode of the NCX during diastole at a lower rate (< 0.5 Hz), and negative inotropism via the inhibition of the L-type calcium channel at a higher rate (> 0.5 Hz) in rat hearts [21]. Therefore, the negative inotropism of propofol observed in this study could be partially due to the inhibition of the L-type calcium channel.

Considering the preserved PVA-independent Vo_2-Emax relationship in the propofol inotropism run in the present study and the enhanced myofilament Ca^{2+} sensitivity reported in the earlier study [4], we can conjecture that propofol has at least 2 effects on myocardial Ca^{2+} handling—namely, a decrease in Emax and an associated decrease in RF. Another possible mechanism preserving the oxygen cost of contractility could be the anti-apoptotic effects of propofol on cardiomyocytes [22] and the resulting protective effect of propofol on endothelial dysfunction, which would improve coronary micro-circulation [23]. Although the present study did not elucidate further details of the individual mechanoenergetic factors, it did help to clarify the overall effects of propofol on the canine heart, which is better than the rodent heart for mimicking human cardiac mechanoenergetics.

Clinical implications. Our present results indicate that propofol has a negative inotropic effect over a wide concentration range, and a non-significant need of any decrement of propofol concentration in the

clinical situation. The present results also suggest that the decrease in blood pressure during anesthetic induction with propofol mainly depends on factors other than cardiac contractility *per se*.

Propofol was found to maintain both the O_2 cost of PVA and the O_2 cost of Emax. These results suggest that the actions of propofol on the heart are quantitatively similar to those of Ca^{2+} blockers or ß-antagonists from the viewpoint of mechanoenergetics [9].

We focused on the effects of propofol on the non-ischemic heart preparation in this study and observed that intracoronary propofol did not significantly change coronary flow at a constant LV volume, even at a higher dosage than is used clinically (Table 1). As for the effect of propofol on coronary circulation, it has been reported that propofol confers protection against ischemic reperfusion injury [24]. On the other hand, propofol has been shown to diminish the protective effects of sevoflurane against ischemic reperfusion injury by activating calcium/calmodulin-dependent protein kinase type II and by hyperphosphorylation of the ryanodine receptor-2, causing a postischemic calcium leakage from the SR [25]. Because coronary flow is determined by multiple factors, such as cardiac contractility (Gregg phenomenon) and production of NO or EDHF, it will be important to further investigate the effects and action mechanisms of propofol under several ischemic conditions to obtain better clinical outcomes.

In conclusion, we assessed the effect of intracoronary propofol on LV mechanoenergetics in excised cross-circulated canine hearts by using the Emax-PVA-Vo_2 relationship. The present results indicated that intracoronary propofol had a negative inotropic effect on the left ventricle without changing the O_2 cost of Emax.

Acknowledgments. We gratefully acknowledge Dr. Hiroyuki Suga for his warm encouragement. This study was partly supported by Grants-in-Aid for Scientific Research (Nos. 13558113, 13770350, 13878185, 13878192, and 14380405) from the Ministry of Education, Science, Technology, Sports and Culture, and a Research Grant for Cardiovascular Diseases (14A-1) from the Ministry of Health, Labor and Welfare of Japan.

References

1. Yang CY, Wong CS, Yu CC, Luk HN and Lin CI: Propofol inhibits cardiac L-type calcium current in guinea pig ventricular myocytes. Anesthesiology (1996) 84: 626–635.
2. Guenoun T, Montagne O, Laplace M and Crozatier B: Propofol-induced modifications of cardiomyocyte calcium transient and sarcoplasmic reticulum function in rats. Anesthesiology (2000) 92: 542–549.
3. Buljubasic N, Marijic J, Berczi V, Supan DF, Kampine JP and Bosnjak ZJ: Differential effects of etomidate, propofol, and midazolam on calcium and potassium channel currents in canine myocardial cells. Anesthesiology (1996) 85: 1092–1099.
4. Kanaya N, Murray PA and Damron DS: Propofol increases myofilament Ca^{2+} sensitivity and intracellular pH via activation of Na^+-H^+ exchange in rat ventricular myocytes. Anesthesiology (2001) 94: 1096–1104.
5. Pagel PS and Warltier DC: Negative inotropic effects of propofol as evaluated by the regional preload recruitable stroke work relationship in chronically instrumented dogs. Anesthesiology (1993) 78: 100–108.
6. Ismail EF, Kim SJ, Salem MR and Crystal GJ: Direct effects of propofol on myocardial contractility in in situ canine hearts. Anesthesiology (1992) 77: 964–972.
7. Nakaigawa Y, Akazawa S, Shimizu R, Ishii R and Yamato R: Effects of graded infusion rates of propofol on cardiovascular haemodynamics, coronary circulation and myocardial metabolism in dogs. Br J Anaesth (1995) 75: 616–621.
8. Ouattara A, Langeron O, Souktani R, Mouren S, Coriat P and Riou B: Myocardial and coronary effects of propofol in rabbits with compensated cardiac hypertrophy. Anesthesiology (2001) 95: 699–707.
9. Suga H: Ventricular energetics. Physiol Rev (1990) 70: 247–277.
10. Suga H, Sagawa K and Shoukas AA: Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. Circ Res (1973) 32: 314–322.
11. Kohno K, Takaki M, Ishioka K, Nakayama Y, Suzuki S, Araki J, Namba T and Suga H: Effects of intracoronary fentanyl on left ventricular mechanoenergetics in the excised cross-circulated canine heart. Anesthesiology (1997) 87: 658–666.
12. Nakayama Y, Takaki M, Kohno K, Araki J and Suga H: Mechanoenergetics of the negative inotropism of isoflurane in the canine left ventricle. No O_2 wasting effect. Anesthesiology (1997) 87: 82–93.
13. England PJ: Cardiac function and phosphorylation of contractile proteins. Philos Trans R Soc Lond B Biol Sci (1983) 302: 83–90.
14. Syuu Y, Araki J, Lee S, Suzuki S, Mizuno J, Mohri S, Mikane T, Shimizu J, Takaki M and Suga H: Effects of Ca^{2+} and epinephrine on Ca^{2+} recirculation fraction and total Ca^{2+} handling in canine left ventricles. Jpn J Physiol (1998) 48: 123–132
15. Shafer A, Doze VA, Shafer SL and White PF: Pharmacokinetics and pharmacodynamics of propofol infusions during general anesthesia. Anesthesiology (1988) 69: 348–356.
16. Suga H, Goto Y, Yasumura Y, Nozawa T, Futaki S, Tanaka N and Uenishi M: O_2 consumption of dog heart under decreased coronary perfusion and propranolol. Am J Physiol (1988) 254: H292–303.
17. Suga H, Hisano R, Goto Y, Yamada O and Igarashi Y: Effect of positive inotropic agents on the relation between oxygen consumption and systolic pressure volume area in canine left ventricle. Circ Res (1983) 53: 306–318.
18. Goto Y, Slinker BK and LeWinter MM: Decreased contractile efficiency and increased nonmechanical energy cost in hyperthyroid rabbit heart. Relation between O_2 consumption and systolic pressure-volume area or force-time integral. Circ Res (1990) 66: 999–

1011.
19. Ohgoshi Y, Goto Y, Futaki S, Yaku H, Kawaguchi O and Suga H: Increased oxygen cost of contractility in stunned myocardium of dog. Circ Res (1991) 69: 975–988.
20. Barry WH and Bridge JH: Intracellular calcium homeostasis in cardiac myocytes. Circulation (1993) 87: 1806–1815.
21. de Ruijter W, Stienen GJ, van Klarenbosch J and de Lange JJ: Negative and positive inotropic effects of propofol via L-type calcium channels and the sodium-calcium exchanger in rat cardiac trabeculae. Anesthesiology (2002) 97: 1146–1155.
22. Lai HC, Yeh YC, Wang LC, Ting CT, Lee WL, Lee HW, Wang KY, Wu A, Su CS and Liu TJ: Propofol ameliorates doxorubicin-induced oxidative stress and cellular apoptosis in rat cardiomyocytes. Toxicol Appl Pharmacol (2011) 257: 437–448.
23. Zhu M, Chen J, Tan Z and Wang J: Propofol protects against high glucose-induced endothelial dysfunction in human umbilical vein endothelial cells. Anesth Analg (2012) 114: 303–309.
24. Kokita N, Hara A, Abiko Y, Arakawa J, Hashizume H and Namiki A: Propofol improves functional and metabolic recovery in ischemic reperfused isolated rat hearts. Anesth Analg (1998) 86: 252–258.
25. Zaugg M, Wang L, Zhang L, Lou PH, Lucchinetti E and Clanachan AS: Choice of anesthetic combination determines Ca^{2+} leak after ischemia-reperfusion injury in the working rat heart: favorable versus adverse combinations. Anesthesiology (2012) 116: 648–657.