

Alterations in Canine Left Ventricular-arterial Coupling and Mechanical Efficiency Produced by Propofol

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Background: Propofol reduces blood pressure by decreasing left ventricular (LV) afterload and myocardial contractility. This investigation tested the hypothesis that propofol preserves LV-arterial coupling and mechanical efficiency because of these simultaneous hemodynamic actions.

Methods: Experiments were conducted in open-chest dogs ($n = 8$) instrumented for measurement of aortic and LV pressure, dp/dt_{max} , and LV volume. Myocardial contractility was assessed with the slope (E_{es}) of the LV end systolic pressure-volume relationship. Effective arterial elastance (E_a ; the ratio of end systolic arterial pressure to stroke volume), stroke work (SW), and pressure-volume area (PVA) were determined from the LV pressure-volume relationships. Dogs were studied 30 min after instrumentation and after 15-min intravenous infusions of propofol at 5, 10, 20, and 40 $mg \cdot kg^{-1} \cdot h^{-1}$.

Results: Propofol caused dose-dependent decreases in E_{es} (4.7 ± 0.9 during control to 2.7 ± 0.5 mmHg/ml during the high dosage) and dp/dt_{max} , indicating a direct negative inotropic effect. E_a increased at the 10 $mg \cdot kg^{-1} \cdot h^{-1}$ dose of propofol but decreased at higher dosages. Propofol decreased the ratio of E_{es} to E_a (0.88 ± 0.13 during control to 0.56 ± 0.10 during the high dosage), consistent with impairment of LV-arterial coupling. Propofol also reduced the ratio SW to PVA (0.54 ± 0.03 during control to 0.45 ± 0.03 during the 20 $mg \cdot kg^{-1} \cdot h^{-1}$), suggesting a decline in LV mechanical efficiency. SW and PVA recovered toward baseline values at the 40 $mg \cdot kg^{-1} \cdot h^{-1}$ dose.

Conclusions: Although propofol depresses mechanical matching of the LV to the arterial system and reduces LV effi-

ciency, these alterations plateau at higher dosages of propofol because reductions in afterload begin to offset further declines in myocardial contractile function. (Key words: Anesthetics, intravenous: propofol. Heart: end systolic pressure-volume relation, left ventricular-arterial coupling; mechanical efficiency; myocardial contractility.)

LEFT ventricular-arterial coupling describes the mechanical relationship between the left ventricle and the arterial system. Overall cardiovascular performance depends on the complex interaction of the systolic and diastolic mechanical properties of the left ventricle and the preload (venous) and afterload (arterial) systems. Changes in the mechanical properties of one system can be compensated by corresponding changes in another system to maintain cardiac output and efficiency. For example, a decrease in left ventricular afterload produced by a vasodilator may preserve cardiac output in the presence of a negative inotropic agent. For any given left ventricular mechanical state there is a unique corresponding mechanical state of the arterial system that will optimize left ventricular performance by maximizing stroke work and minimizing myocardial oxygen consumption. Left ventricular-arterial coupling often is quantified in the pressure-volume plane using a series elastic chamber model of the cardiovascular system.¹ The ratio of the elastances of the left ventricle (end systolic elastance; E_{es}) and the arterial vasculature (effective arterial elastance; E_a) defines coupling between the heart and the arterial circulation.^{1,2} This model allows evaluation of the effects of cardiac disease states and vasoactive drugs on the coupling relationship *in vivo*.^{3,4} Pressure-volume analysis also permits examination of left ventricular mechanical efficiency defined by the ratio of stroke work (SW) to pressure-volume area (PVA).^{3,5}

The effects of propofol on systemic hemodynamics,^{6,7} left ventricular systolic⁸ and diastolic function,⁹ and afterload mechanics¹⁰ *in vivo* have been described previously. Propofol produces dose-related decreases in ar-

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terial blood pressure in part by causing simultaneous reductions in myocardial contractility and arterial vasodilation. These data suggest that left ventricular-arterial coupling may be preserved during propofol anesthesia. The present investigation tested the hypothesis that optimal mechanical interaction between the left ventricle and the arterial system is maintained during intravenous infusions of propofol.

Materials and Methods

All experimental procedures and protocols used in this investigation were reviewed and approved by the Animal Care and Use Committee of the Medical College of Wisconsin. All procedures conformed to the *Guiding Principles in the Care and Use of Animals* of the American Physiological Society and were performed according to the *Guide for the Care and Use of Laboratory Animals*, [DHEW(DHHS) publication (NIH) no. 85-23, revised 1996].

Implantation of Instruments

The experimental preparation used in this investigation has been described previously in detail.¹¹ Briefly, dogs ($n = 8$) were fasted overnight and anesthetized with sodium pentobarbital (25 mg/kg) and sodium barbital (200 mg/kg). Fluid deficits were replaced before experimentation with saline, 0.9% (500 ml), which was continued at $3 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for the duration of each experiment. A pilot study demonstrated that this fluid replacement regimen maintained constant left ventricular end diastolic pressure during administration of propofol in barbiturate-anesthetized dogs. After tracheal intubation, each dog's lungs were ventilated *via* positive pressure with 100% oxygen. Respiratory rate and tidal volume were adjusted to maintain acid-base status and carbon dioxide partial pressure within physiologic limits. The right femoral vein was cannulated for fluid administration. A 7-French, dual micromanometer-tipped catheter was placed across the aortic valve for measurement of continuous left ventricular and arterial pressures and the peak rate of increase of left ventricular pressure (dP/dt_{\max}). A left fifth space thoracotomy was performed, and the lungs were gently retracted. A 7-French, eight-electrode conductance catheter was inserted into the left ventricular cavity through the apex. A hydraulic vascular occluder was placed around the inferior vena cava for abrupt alteration of preload. A fluid-filled catheter was placed in the left atrial append-

age for administration of hypertonic saline (20%; 5 ml) used to determine parallel conductance volume (V_p). The experimental preparation was allowed to stabilize for 30 min after instrumentation had been completed.

Determination of Left Ventricular Volume

Left ventricular volume was measured using the conductance technique.¹² Briefly, a multielectrode conductance catheter was interfaced to a module that drove a constant current between the two outermost electrodes and measured the resultant voltage difference between each of the five remaining adjacent remaining electrode pairs. Time-dependent left ventricular volume $[V(t)]$ was determined using the equation: $V(t) = G(t) \cdot L^2 \cdot (\alpha \cdot \sigma)^{-1} - V_p$, where $G(t)$ = the sum of time-dependent conductances from each intraventricular electrode pair, L = the intraelectrode distance (1.0 cm), α = a slope correction factor relating the measured conductance volume to actual left ventricular volume, and σ = the blood conductivity. The parallel conductance volume (V_p) is a constant offset error volume that results from current leakage into surrounding tissue and was determined using the hypertonic saline technique.^{12,13} No changes in V_p were observed during the administration of propofol. Blood conductivity (σ) was determined at each intervention from a 5-ml blood sample using a cuvette that was precalibrated with solutions of known conductivity. No changes in σ were observed during the course of each experiment. End systolic and end diastolic volumes (ESV and EDV, respectively) were measured at left ventricular maximum elastance¹⁴ and immediately before the onset of left ventricular isovolumic contraction, respectively. Hemodynamic variables were determined at steady-state and averaged for 10 consecutive beats just before caval occlusion. Ejection fraction (EF) was determined using the equation: $EF = (EDV - ESV) \cdot 100 \cdot EDV^{-1}$. Hemodynamic data were continuously recorded on a polygraph and simultaneously digitized (200 Hz) by a computer interfaced with an analog to digital converter for recording and subsequent analysis of left ventricular pressure-volume diagrams.

Experimental Protocol

Left ventricular pressure-volume diagrams used to assess myocardial contractility were obtained at end expiration by abruptly decreasing left ventricular preload via inflation of the inferior vena caval balloon cuff occluder (fig. 1). Using linear regression analysis, the end systolic pressure (P_{es}) and volume (V_{es}) of each left ventricular pressure-volume diagram were fit to the equation: $P_{es} = E_{es} \cdot (V_{es} - V_0)$, where E_{es} = left ventricular end systolic elastance and V_0 = the extrapolated volume intercept of

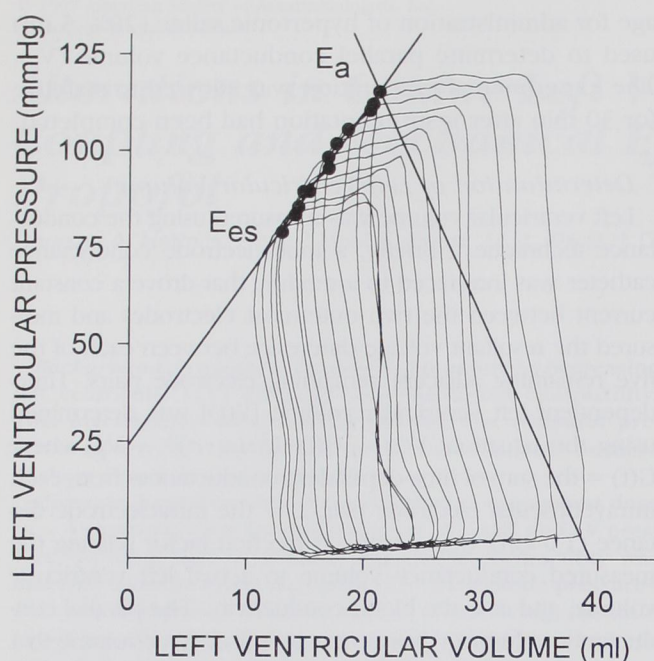


Fig. 1. Left ventricular pressure-volume diagrams obtained during inferior vena caval occlusion obtained in a typical experiment. Left ventricular maximal elastances (solid dots) for each pressure-volume diagram were used to generate the slope (E_{es}) of the end systolic pressure-volume relation. Effective arterial elastance (negative slope, E_a) was determined by the ratio of end systolic arterial pressure and stroke volume during steady-state hemodynamic conditions.

the relation. Myocardial contractility also was evaluated with the slope (M_{sw}) of the preload recruitable stroke work relation derived from the same left ventricular pressure-volume diagrams.¹⁵ Effective arterial elastance (E_a) was calculated as the ratio of end systolic arterial pressure and stroke volume.^{1,2} Figure 1 shows representations of E_{es} and E_a in the pressure-volume plane. Left ventricular-arterial coupling was described by the ratio of E_{es} and E_a .¹ PVA (total mechanical energy) was determined as the sum of SW and potential energy (PE), where $PE = 0.5 \cdot P_{es} \cdot (V_{es} - V_0)$.¹⁶ PE represents left ventricular energy that does not contribute to ejection. The ratio of SW to PVA was used to determine left ventricular mechanical efficiency.⁵

Baseline systemic hemodynamics and left ventricular pressure-volume diagrams were recorded during steady-state conditions 30 min after instrumentation was completed. Propofol then was administered as an intravenous infusion at 5, 10, 20, and 40 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ in escalating dosages. Hemodynamics were recorded, and left ventricular pressure-volume diagrams were obtained using the techniques described previously after 15 min equilibration at each dose. At the end of each

experiment, the heart was electrically fibrillated, and the positions of the fluid-filled, conductance, and micro-manometer-tipped catheters were confirmed.

Statistical Analysis

Statistical analysis of the data before and during administration of propofol was performed by analysis of variance (ANOVA) with repeated measures followed by Student's *t* test with Duncan's adjustment for multiplicity. Changes between interventions were considered statistically significant when the probability (*P*) value was less than 0.05. All data are expressed as mean \pm SEM.

Results

The hemodynamic effects of propofol are summarized in table 1. Propofol caused significant ($P < 0.05$) decreases in heart rate, mean arterial pressure, and left ventricular systolic pressure. Increases in EDV and ESV also were observed at higher dosages. Left ventricular end diastolic pressure remained unchanged. Reductions in E_{es} (4.7 ± 0.9 during control to 2.7 ± 0.5 mmHg/ml during the high dose) and M_{sw} (66 ± 6 during control to 43 ± 5 mmHg during the high dose) were observed during administration of propofol, indicating a direct negative inotropic effect. Concomitant reductions in dP/dt_{max} and ejection fraction also occurred. The volume intercepts of the end systolic pressure-volume (V_0) and preload recruitable stroke work (V_{sw}) relations were unchanged. Propofol caused reductions in SW and PVA at the 40 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ dose. An increase followed by a decrease in E_a was observed at the 10 and 40 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ doses of propofol, respectively. The ratio of E_{es} to E_a was decreased by propofol (0.88 ± 0.13 during control to 0.56 ± 0.10 during the high dose; fig. 2A), indicating that this intravenous anesthetic impairs the mechanical interaction between the left ventricle and the arterial circulation. Propofol also reduced the ratio of SW to PVA (0.54 ± 0.03 during control to 0.45 ± 0.03 during the 20 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ dose; fig. 2B), consistent with a decline in the conversion of total left ventricular energy to external stroke work. However, SW and PVA increased toward control values at the highest dosage of propofol, suggesting that partial restoration of left ventricular mechanical efficiency had occurred.

Discussion

The present results indicate that propofol reduces myocardial contractility as evaluated by E_{es} and M_{sw} derived

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Table 1. Hemodynamic Effects of Propofol

	Control	Propofol (mg · kg ⁻¹ · hr ⁻¹)			
		5	10	20	40
HR (beats · min ⁻¹)	136 ± 4	130 ± 3	124 ± 3*	119 ± 3*,†	100 ± 4*,†,‡,§
MAP (mmHg)	95 ± 4	98 ± 4	103 ± 4	96 ± 5	72 ± 7*,†,‡,§
LVSP (mmHg)	109 ± 3	110 ± 4	114 ± 4	110 ± 5	84 ± 6*,†,‡,§
LVEDP (mmHg)	4 ± 0	3 ± 0	3 ± 0	3 ± 0	3 ± 0
dP/dt _{max} (mmHg · s ⁻¹)	1,829 ± 82	1,690 ± 67	1,634 ± 63*	1,524 ± 79*	1104 ± 97*,†,‡,§
EDV (ml)	48 ± 3	47 ± 3	49 ± 3	50 ± 3	52 ± 2*,†,‡
ESV (ml)	27 ± 2	28 ± 2	29 ± 3*	30 ± 3*	33 ± 3*,†,‡,§
SV (ml)	21 ± 1	19 ± 1	19 ± 2	18 ± 2	20 ± 2
EF (%)	44 ± 3	41 ± 2	40 ± 3*	39 ± 3*	36 ± 3*,†
M _{sw} (mmHg)	66 ± 6	60 ± 6	58 ± 6	53 ± 6*	43 ± 5*,†,‡
V _{sw} (ml)	13 ± 6	14 ± 5	13 ± 6	14 ± 6	17 ± 7
E _{es} (mmHg · ml ⁻¹)	4.7 ± 0.9	4.3 ± 0.8	3.7 ± 0.7	3.2 ± 0.5*	2.7 ± 0.5*,†
V _o (ml)	1.7 ± 4.9	6.4 ± 6.6	4.9 ± 4.1	6.0 ± 5.4	1.9 ± 4.9
E _a (mmHg · ml ⁻¹)	5.3 ± 0.3	6.0 ± 0.3	6.3 ± 0.5*	6.0 ± 0.6	5.1 ± 0.6†,‡,§
SW (ml · mmHg)	1,704 ± 118	1,583 ± 119	1,652 ± 158	1,562 ± 162	1,214 ± 170*,†,‡,§
PVA (ml · mmHg)	3,302 ± 366	3,618 ± 548	3,730 ± 428	3,619 ± 448	2,601 ± 319*,†,‡,§

Data are mean ± SEM; n = 8.

HR = heart rate; MAP = mean arterial pressure; LVSP = left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; EDV and ESV = end-diastolic and end-systolic volume, respectively; SV = stroke volume; EF = ejection fraction; M_{sw} and V_{sw} = preload recruitable stroke work slope and volume intercept, respectively; E_{es} = end-systolic elastance; V_o = volume intercept; E_a = effective arterial elastance; SW = stroke work area; PVA = pressure volume area.

* Significantly ($P < 0.05$) different from control.

† Significantly ($P < 0.05$) different from 5 mg · kg⁻¹ · hr⁻¹ propofol.

‡ Significantly ($P < 0.05$) different from 10 mg · kg⁻¹ · hr⁻¹ propofol.

§ Significantly ($P < 0.05$) different from 20 mg · kg⁻¹ · hr⁻¹ propofol.

from left ventricular pressure-volume diagrams generated using the conductance catheter. The present findings confirm and extend the findings from a previous investigation from our laboratory,⁸ in which regional preload recruitable SW derived from subendocardial segment length was used as a relatively heart rate- and load-independent index of contractile state before and during propofol anesthesia in chronically instrumented dogs. E_a increased slightly at the 10 mg · kg⁻¹ · h⁻¹ dose and then decreased with higher dosages of propofol. E_a is closely related to left ventricular afterload because this coupling variable directly depends on systemic vascular resistance and inversely depends on total arterial compliance. The present results are consistent with previous findings from this^{8,10} and other laboratories,¹⁷⁻¹⁹ indicating that propofol does not alter indices of left ventricular afterload (e.g., systemic vascular resistance and aortic input impedance) in dogs despite producing dose-related depression of myocardial contractility at very low dosages of propofol similar to those used in the present study. In contrast, propofol reduces afterload at higher dosages concomitant with additional negative ino-

tropic effects.^{8,10,17} These observations have important implications for left ventricular-arterial coupling relations.

The present investigation examined the effects of propofol on left ventricular-arterial coupling using a series elastic chamber model quantified by the ratio of E_{es} to E_a.^{1,2} It has been shown that SW is maximized when E_a is equal to E_{es}.¹ The results indicate that propofol decreases E_{es}/E_a, indicating that this intravenous anesthetic impairs mechanical coupling of the left ventricle to the arterial vasculature. These propofol-induced reductions in E_{es}/E_a result from primary decreases in E_{es}. At higher dosages of propofol (20 and 40 mg · kg⁻¹ · h⁻¹), E_{es}/E_a plateaus and does not decrease further because modest reductions in E_a offset further declines in contractility. This finding indicates that left ventricular-arterial coupling is not restricted at higher doses of propofol despite dose-related decreases in E_{es}. The present results with propofol contrast with a previous investigation examining the influence of desflurane, isoflurane, and sevoflurane on left ventricular-arterial coupling in barbiturate-anesthetized dogs.¹¹ These volatile anesthetics decreased E_{es} and E_a in a dose-related manner. However, because vola-

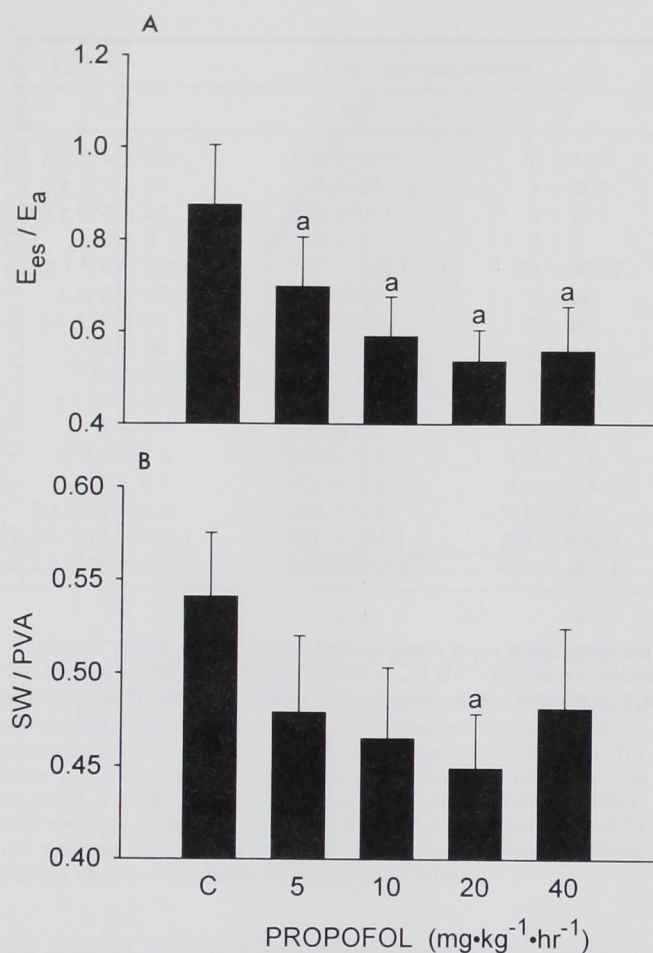


Fig. 2. Histograms depicting (A) left ventricular-arterial coupling (E_{es}/E_a) and (B) left ventricular mechanical efficiency (SW/PVA) before (control; C) and during 5, 10, 20, and 40 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ propofol infusions. Data are mean \pm SEM; $n = 8$. ^aSignificantly ($P < 0.05$) different from C.

tile anesthetic-induced declines in E_{es} were proportionally greater than E_a , the ratio of E_{es} to E_a also declined in a dose-dependent manner.

The effects of propofol on the efficiency of energy transfer from the left ventricle to the arterial system also were quantified in the present investigation using the ratio of SW to PVA. PVA represents the amount of work performed by the left ventricle and is defined as the sum of SW (kinetic energy that contributes to ejection) and potential energy (energy used to overcome the viscoelastic and inertial properties of the myocardium itself).^{5,20} Decreases in SW and PVA imply less efficient energy transfer from the left ventricle to the arterial system. The present results indicate the propofol reduces SW and PVA at the intermediate dosages,

although these declines in SW and PVA were reversed to some degree at the 40 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ dose. This finding parallels the observations with E_{es} and E_a and suggests that modest reductions in afterload produced by propofol also may limit declines in left ventricular mechanical efficiency at higher dosages. The predominant hemodynamic effect of lower dosages of propofol is a reduction in myocardial contractile function with little change in afterload, resulting in deleterious declines in left ventricular-arterial coupling. This was not the case in our previous study, in which desflurane, isoflurane, and sevoflurane caused dose-related reductions in SW and PVA.¹¹ Maintenance of stroke volume may be one of the important benefits of preserving left ventricular-arterial coupling relationships. Stroke volume remained constant at all dosages of propofol.

The present results require interpretation within the constraints of several potential limitations. The cardiovascular depression associated with barbiturate anesthesia and acute surgical instrumentation may prevent direct comparison of the present results with those obtained in conscious, chronically instrumented dogs. The negative inotropic effects of sodium barbital and sodium pentobarbital may have resulted in greater decreases in contractility with propofol in the present study than observed previously.⁸ However, reductions in M_{sw} during the 40 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ dose of propofol in the present study (approximately 65% of control) were similar to those observed with 30 and 60 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ doses (approximately 68% and 60%, respectively) in a previous investigation, in which chronically instrumented dogs were used.⁸ These data indicate that the baseline barbiturate anesthetic did not substantially alter the effects of propofol on myocardial contractility. The value of E_{es} and E_a observed during control steady-state hemodynamic conditions also was similar to that observed in conscious dogs,⁴ suggesting the barbiturate-induced alterations in left ventricular-arterial coupling did not adversely influence the effects of propofol on this relation. Nevertheless, the possibility of drug interactions between the barbiturate anesthetics and propofol in this investigation cannot be completely excluded from interpretation of the results. Lack of a conscious control state also impairs direct comparison of the present and previous results.

The slope of the end systolic pressure-volume relation has been shown to be curvilinear for a range of pressures.²¹ However, this relation has been established to be linear²² for the relatively narrow range of left ventricular pressures observed during interior vena ca-

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val occlusion in the present investigation. E_{es} and V_0 may be underestimated using the conductance catheter technique to measure left ventricular volume,²³ but alterations in E_{es} in response to vasoactive drugs were appropriately quantified with the conductance technique when compared with three-dimensional sonomicrometry.²³ Thus, it is likely that propofol-induced negative inotropic effects were accurately measured using conductance catheter-derived left ventricular volume data. The determination of stroke volume required for the calculation of E_a using the conductance technique also has been validated previously.^{12,13}

The dosages of propofol used in the present investigation were chosen because these doses produce corresponding plasma concentrations that fall within the anesthetic range in humans. The 20 and 40 mg · kg⁻¹ · h⁻¹ doses of propofol produce plasma concentrations between 2 and 13 µg/ml in dogs¹⁷ that correlate with clinically relevant concentrations. Nevertheless, comparison of the effects of propofol on systemic hemodynamics, myocardial contractility, and left ventricular-arterial coupling relations between barbiturate-anesthetized dogs and humans can be inferred only indirectly.

In summary, the present investigation demonstrated that propofol reduces optimal left ventricular-arterial coupling and mechanical efficiency as evaluated by E_{es} and E_a and SW and PVA, respectively. These detrimental effects plateau at higher doses of propofol because declines in afterload occur that partially offset depression of myocardial contractility. Propofol-induced impairment in left ventricular-arterial coupling may contribute to declines in overall cardiovascular performance observed with this anesthetic *in vivo*.

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References

1. Sunagawa K, Maughan WL, Burkhoff D, Sagawa K: Left ventricular interaction with arterial load studied in isolated canine ventricle. *Am J Physiol* 1983; 245:H773-80
2. Sunagawa K, Maughan WL, Sagawa K: Optimal arterial resistance for the maximal stroke work studied in isolated canine left ventricle. *Circ Res* 1985; 56:586-95
3. Starling MR: Left ventricular-arterial coupling relations in the normal human heart. *Am Heart J* 1993; 125:1659-66
4. Little WC, Cheng C-P: Left ventricular-arterial coupling in conscious dogs. *Am J Physiol* 1991; 261:H70-6
5. Burkhoff D, Sagawa K: Ventricular efficiency predicted by an analytical model. *Am J Physiol* 1986; 250:R1021-R7
6. Sebel PS, Lowdon JD: Propofol: A new intravenous anesthetic. *ANESTHESIOLOGY* 1989; 71:260-77
7. Smith I, White PF, Nathanson M, Gouldson R: Propofol. An update on its clinical use. *ANESTHESIOLOGY* 1994; 81:1005-43
8. Pagel PS, Warltier DC: Negative inotropic effects of propofol as evaluated by the regional preload recruitable stroke work relationship in chronically instrumented dogs. *ANESTHESIOLOGY* 1993; 78:100-8
9. Pagel PS, Schmeling WT, Kampine JP, Warltier DC: Alteration of canine left ventricular diastolic function by intravenous anesthetics *in vivo*. Ketamine and propofol. *ANESTHESIOLOGY* 1992; 76:419-25
10. Lowe D, Hettrick DA, Pagel PS, Warltier DC: Propofol alters left ventricular afterload as evaluated by aortic input impedance in dogs. *ANESTHESIOLOGY* 1996; 84:368-76
11. Hettrick DA, Pagel PS, Warltier DC: Desflurane, sevoflurane, and isoflurane impair canine left ventricular-arterial coupling and mechanical efficiency. *ANESTHESIOLOGY* 1996; 85:403-13
12. Baan J, Jong TT, Kerkof PLM, Moene RJ, Van Dijk AD, Van der Velde ET, Koops J: Continuous stroke volume and cardiac output from intra-ventricular dimensions obtained with impedance catheter. *Cardiovasc Res* 1981; 15:328-34
13. Baan J, Van der Velde ET, De Bruin HG, Smeenk GJ, Koops J, van Dijk AD, Temmerman D, Senden J, Buis B: Continuous measurement of left ventricular volume in animals and humans by conductance catheter. *Circulation* 1984; 70:812-23
14. Suga H, Sagawa K: Instantaneous pressure-volume relationships and their ratio in the excised, supported canine left ventricle. *Circ Res* 1974; 35:117-26
15. Glower DD, Spratt JA, Snow ND, Kabas JS, Davis HW, Olsen CO, Tyson GS, Sabiston Jr DC, Rankin JS: Linearity of the Frank-Starling relationship in the intact heart: The concept of preload recruitable stroke work. *Circulation* 1985; 71:994-1009
16. Sagawa K, Maughan L, Suga H, Sunagawa K: Cardiac contraction and the pressure-volume relationship. New York, Oxford University Press, 1988, pp 171
17. Goodchild CS, Serrao JM: Cardiovascular effects of propofol in the anesthetized dog. *Br J Anaesth* 1989; 63:87-92
18. Coetzee A, Fourie P, Coetzee J, Badenhorst E, Rebel A, Bolliger C, Uebel R, Wium C, Lombard C: Effect of various propofol plasma concentrations on regional myocardial contractility and left ventricular afterload. *Anesth Analg* 1989; 69:473-83
19. Brussel T, Theissen JL, Vigfusson G, Lunkenheimer PP, Van Aken, Lawin P: Hemodynamic and cardiodynamic effects of propofol and etomidate: Negative inotropic properties of propofol. *Anesth Analg* 1989; 69:35-40
20. Denslow S: Relationship between PVA and myocardial oxygen consumption can be derived from thermodynamics. *Am J Physiol* 1996; 270:H730-H40
21. Kass DA, Beyar R, Lankford E, Heard M, Maughan WL, Sagawa K: Influence of contractile state on curvilinearity of *in situ* end-systolic pressure-volume relations. *Circulation* 1989; 79:167-78
22. Little WC, Cheng CP, Peterson T, Vinten-Johansen J: Response of the left ventricular end-systolic pressure-volume relation in conscious dogs to a wide range of contractile states. *Circulation* 1988; 78:736-45
23. Applegate RJ, Cheng C-P, Little WC: Simultaneous conductance catheter and dimension assessment of left ventricle volume in the intact animal. *Circulation* 1990; 81:638-48