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Cardiovascular Effects of Propofol in Dogs with Dilated Cardiomyopathy

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Background: **The authors tested the hypothesis that propofol improves left ventricular diastolic function in dogs with dilated cardiomyopathy by reducing left ventricular preload and afterload.**

Methods: **Seven dogs were instrumented for left ventricular and aortic pressures, aortic blood flow, and subendocardial segment length. Left ventricular afterload and contractility were quantified with aortic input impedance and preload recruitable stroke work, respectively. Diastolic function was evaluated with a time constant of left ventricular relaxation (τ); segment-lengthening velocities and time–velocity integrals during early left ventricular filling (dL/dt_E and TVI-E, respectively) and atrial systole (dL/dt_A and TVI-A, respectively); and a regional chamber stiffness constant (K). Dogs were paced at 240 beats/min for 18 ± 3 days, and hemodynamics were recorded in sinus rhythm in the conscious state. Anesthesia was induced with propofol (5 mg/kg) and maintained with propofol infusions at 25, 50, and 100 $mg \cdot kg^{-1} \cdot h^{-1}$, and hemodynamics were recorded after 15 min of equilibration at each dose.**

Results: **Propofol decreased mean arterial pressure, left ventricular end-diastolic pressure, and K but did not change heart rate. Propofol reduced total arterial resistance and increased total arterial compliance derived from aortic input impedance. Propofol also reduced preload recruitable stroke work. The lowest dose of propofol decreased τ. Propofol decreased dL/dt_E and TVI-E and reduced the dL/dt-E/A and TVI-E/A ratios.**

Conclusions: **Propofol reduces left ventricular preload, afterload, and regional chamber stiffness, causes direct negative inotropic effects, and impairs early-diastolic left ventricular filling in dogs with dilated cardiomyopathy. (Key words: Diastolic function; heart failure; isovolumic relaxation; left ventricular afterload; myocardial contractility; power spectrum analysis; preload recruitable stroke work; rapid ventricular filling.)**

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THE cardiovascular effects of propofol during anesthesia[1] in patients with normal cardiac performance have been attributed to the combined actions of decreases in left ventricular (LV) preload and afterload produced by venous[2] and arterial vasodilation,[3] inhibition of sympathetic nervous system activity,[4–6] and impairment of baroreceptor-mediated reflexes.[4–6] Propofol-induced myocardial depression has also been implicated in the declines in arterial pressure and cardiac output produced by this anesthetic, although the relative contribution of this negative inotropic effect to the reduction of arterial pressure has been debated intensely. Several studies have shown that propofol produces modest decreases in myocardial contractility in normal cardiac muscle *in vitro*[7–9] and *in vivo*[10–12]; however, other studies have failed to demonstrate this negative inotropic effect.[13,14] Although the actions of propofol on LV systolic performance are somewhat controversial, propofol has been shown to preserve indices of LV diastolic function in healthy dogs,[15] even at doses that would be supratherapeutic in humans. It is unlikely, therefore, that abnormalities in LV diastolic function contribute to the cardiovascular effects of propofol in the healthy heart.

The hemodynamic effects of propofol in patients with mildly compromised LV function undergoing coronary

artery bypass surgery[16-19] are similar to those described in patients with normal cardiac performance, but the precise cardiovascular actions of propofol in the presence of severe LV dysfunction are unknown. Recent studies in isolated ventricular myocytes[20] and LV trabecular muscle[21] obtained from pigs with pacing-induced cardiomyopathy and explanted failing hearts of human recipients of cardiac transplants, respectively, have demonstrated that propofol causes direct negative inotropic effects that may be more pronounced than those produced by this intravenous anesthetic in normal myocardium. Despite the finding that these results have not been uniformly supported,[22] extrapolation of these results[20,21] to the intact cardiovascular system suggests that depression of myocardial contractility may play a more important role in determining the hemodynamic effects of propofol in the setting of congestive heart failure. The influence of propofol on LV diastolic mechanics also has not been described in the failing heart. Further, propofol has been shown to produce unique, beneficial effects on total arterial resistance and total arterial compliance determined from aortic input impedance ($Z_{in}[\omega]$) spectra in healthy dogs,[3] but whether these favorable alterations in the determinants of LV afterload are preserved during anesthesia with propofol in the presence of LV dysfunction are unknown.

The current investigation examined the cardiovascular effects of propofol on systemic and coronary hemodynamics, $Z_{in}(\omega)$, and LV systolic and diastolic function in a model of chronically instrumented canines with LV dysfunction produced by rapid LV pacing. We[23,24] and others[25-27] have shown that 3 weeks of rapid LV pacing causes progressive biventricular dilation with increased filling pressures and pronounced LV systolic and diastolic dysfunction but without frank congestive heart failure. The current investigation tested the hypothesis that propofol results in improvements in LV diastolic function by causing reductions in LV preload and afterload despite producing simultaneous negative inotropic effects in dogs with dilated cardiomyopathy.

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 in accordance with the *Guide for the Care and Use of Laboratory Animals.*

Experimental Model

The surgical implantation of instruments has been described in detail previously.[23] Briefly, in the presence of general anesthesia and using aseptic techniques, a left thoracotomy was performed in conditioned mongrel dogs for placement of instruments for measurement of aortic, left atrial, and intrathoracic pressures (heparin–filled catheters); aortic blood flow (Doppler flow transducer); left anterior descending coronary artery blood flow velocity (ultrasonic flow transducer); subendocardial segment length (ultrasonic crystals); LV pressure (high fidelity, miniature micromanometer); and the peak rates of increases and decreases in LV pressure (dP/dt_{max} and $-dP/dt_{min}$, respectively). A hydraulic vascular occluder was placed around the inferior vena cava for abrupt reduction of LV preload. Stainless steel pacing electrodes were sutured to the epicardial surface of the LV free wall. All instruments were firmly secured, tunneled between the scapulae, and exteriorized via several small incisions. The pericardium was left open wide, the chest wall was closed in layers, and the pneumothorax was evacuated by a chest tube. Each dog was fitted with a jacket to prevent damage to the instruments, catheters, and pacing electrodes.

All dogs received fentanyl for analgesia as needed after surgery. Dogs were allowed to recover for a minimum of 7 days before experimentation, during which time all were treated with intramuscular antibiotic agents (cephalothin at 40 mg/kg and gentamicin at 4.5 mg/kg) and trained to stand quietly in a sling during hemodynamic monitoring. Segment length and coronary blood flow velocity signals were monitored by ultrasonic amplifiers. End-systolic and end-diastolic segment lengths were measured 30 ms before LV $-dP/dt_{min}$ and immediately before the onset of LV isovolumic contraction, respectively. Percent segment shortening (%SS) was determined using the equation $\%SS = (EDL - ESL) \cdot 100 \cdot EDL^{-1}$. Relative diastolic coronary vascular resistance was calculated as the quotient of diastolic arterial pressure to diastolic coronary blood flow velocity. An estimate of myocardial oxygen consumption, the pressure-work index, was determined using a previously validated formula.[28] Hemodynamic data were recorded continuously on a polygraph and simultaneously digitized and recorded on a computer.

Experimental Protocol

After each dog (n = 7; mean ± SEM weight, 25.3 ± 0.4 kg) had recovered from surgery, the LV of the dog was paced continuously at rates between 220 and 240 beats/min as previously described.[23] Dogs were brought to the laboratory on each day after the initiation of pacing to monitor the development of pacing-induced cardiomyopathy. Pacing was discontinued during and restarted immediately after this brief period of daily hemodynamic monitoring and was discontinued for the duration of the experiment. All dogs were fasted overnight before experimentation. Fluid deficits were replaced with 0.9% saline (500 ml), and intravenous saline infusion was continued at 3 $ml \cdot kg^{-1} \cdot h^{-1}$ for the duration of each experiment.

After instruments were calibrated, baseline systemic and coronary hemodynamics were recorded in the conscious state (sinus rhythm). Left ventricular and intrathoracic pressures and segment length waveforms also were recorded for later off-line analysis of LV systolic and diastolic function. Regional myocardial contractility was evaluated using a series of LV pressure-segment length diagrams generated by abrupt inferior vena cava constriction as previously described.[23] The slope of the regional preload recruitable stroke work (M_W) relation derived from these LV pressure-segment length diagrams was used to quantify myocardial contractility. The time constant of LV isovolumic relaxation (τ) was calculated using the derivative method. Segment-lengthening velocities during early ventricular filling (dL/dt_E) and atrial systole (dL/dt_A) and their corresponding time-velocity integrals (TVI-E and TVI-A, respectively) were determined from the continuous dL/dt waveform. Early ventricular filling fraction was calculated as the fraction of total segment lengthening occurring during early ventricular filling. A regional chamber stiffness constant (K) was derived from LV pressure-segment length data between minimum ventricular pressure and the beginning of atrial systole using a monoexponential relation assuming a simple elastic model.

Left ventricular afterload was quantified with $Z_{in}(\omega)$ spectra and interpreted using a three-element Windkessel model of the arterial circulation as previously described.[29] Briefly, digitized, steady-state aortic blood pressure and blood flow waveforms were transformed from the time to the frequency (ω) domain using power spectral analysis to determine $Z_{in}(\omega)$. The autopower spectrums of aortic pressure ($P_{pp}[\omega]$) and blood flow ($P_{ff}[\omega]$) and the crosspower spectrum between aortic pressure and blood flow waveforms ($P_{pf}[\omega]$) were determined using a Welch periodogram, and $Z_{in}(\omega)$ was calculated as the ratio of $P_{pp}(\omega)$ to $P_{pf}(\omega)$. Each calculated $Z_{in}(\omega)$ spectrum was corrected for the phase responses of the aortic pressure and blood flow transducers. Correlation of aortic pressure and blood flow waveforms at each frequency of the $Z_{in}(\omega)$ spectrum was determined using magnitude squared coherence. $Z_{in}(\omega)$ data with magnitude squared coherence values <0.8 were discarded from the analysis. Characteristic aortic impedance (Z_C) was determined as the magnitude of $Z_{in}(\omega)$ between 2 and 15 Hz. Total arterial resistance (R) was calculated as the difference between $Z_{in}(\omega)$ at 0 Hz and Z_C. Total arterial compliance (C) was determined from aortic pressure and blood flow waveforms using a previously validated formula.[30]

Anesthesia was induced with 5 mg/kg of intravenous propofol and maintained with propofol infusions at 25, 50, and 100 $mg \cdot kg^{-1} \cdot h^{-1}$ administered in a sequential manner. The lungs of each dog were mechanically ventilated with oxygen-supplemented air (25% oxygen). Arterial blood gas tensions were maintained at levels obtained in the conscious state by adjustment of air and oxygen concentrations and respiratory rate throughout each experiment. Systemic and coronary hemodynamics and LV pressure, intrathoracic pressure, aortic pressure, aortic blood flow, and myocardial segment length waveforms were recorded under steady-state conditions and during inferior vena cava occlusion at end expiration after 15 min of equilibration at each propofol infusion rate. Thus, the effects of propofol on LV systolic and diastolic function and LV afterload were compared with data observed in the conscious state in chronically instrumented dogs with pacing-induced cardiomyopathy.

Statistical Analysis

Statistical analysis of the data in the conscious state and during propofol anesthesia was performed by analysis of variance with repeated measures, followed by use of Student's *t* test with Duncan's adjustment for multiplicity. A probability value < 0.05 was considered statistically significant. All data are expressed as mean ± SEM.

Results

The hemodynamic effects of propofol in dogs with pacing-induced cardiomyopathy are summarized in table 1. Propofol caused significant and dose-related

Table 1. Hemodynamic Effects of Propofol

	Conscious	Propofol ($mg \cdot kg^{-1} \cdot h^{-1}$)		
		25	50	100
HR (bpm)	90 ± 6	89 ± 9	93 ± 9	92 ± 6
MAP (mmHg)	94 ± 2	81 ± 6*	76 ± 7*	55 ± 5*†‡
RPP ($mmHg \cdot bpm \cdot 10^3$)	10.3 ± 0.7	8.9 ± 1.3	8.6 ± 1.3	6.3 ± 0.4*†
LVSP (mmHg)	110 ± 5	94 ± 4*	86 ± 5*	67 ± 5*†‡
LVEDP (mmHg)	24 ± 2	16 ± 2*	15 ± 2*	13 ± 2*†
DCBFV ($Hz \cdot 10^2$)	60 ± 11	53 ± 9	53 ± 9	52 ± 10
DCVR ($mmHg \cdot Hz^{-1} \cdot 10^{-2}$)	1.64 ± 0.24	1.60 ± 0.29	1.46 ± 0.23	1.13 ± 0.19*†‡
$+dP/dt_{max}$ ($mmHg \cdot s^{-1}$)	1,584 ± 49	1,305 ± 50*	1,213 ± 80*	919 ± 74*†‡
$-dP/dt_{min}$ ($mmHg \cdot s^{-1}$)	−1,660 ± 75	−1,363 ± 55*	−1,264 ± 74*	−967 ± 80*†‡
EDL (mm)	27.5 ± 2.5	26.5 ± 2.4*	26.5 ± 2.5*	25.4 ± 2.4*†‡
EEVFL (mm)	26.2 ± 2.5	24.9 ± 2.5*	24.9 ± 2.5*	24.1 ± 2.4*†‡
ESL (mm)	21.6 ± 2.4	21.3 ± 2.3	21.2 ± 2.4	20.9 ± 2.2*
SS (%)	21.8 ± 2.7	20.1 ± 2.8	20.2 ± 3.3	17.9 ± 2.6*
EVFF (%)	78.5 ± 3.0	69.1 ± 3.2*	67.9 ± 4.3*	68.7 ± 3.2*
L_w (mm)	19.9 ± 2.3	18.8 ± 2.8	18.7 ± 2.1	17.7 ± 1.7*
MAQ ($L \cdot min^{-1}$)	2.14 ± 0.25	1.85 ± 0.19*	1.77 ± 0.16*	1.47 ± 0.17*†
SV (ml)	24 ± 3	21 ± 3	19 ± 2*	16 ± 2*†
PWI ($ml \cdot min^{-1}$ 100 g^{-1})	8.5 ± 0.5	7.5 ± 0.7	7.2 ± 0.7	5.2 ± 0.4*†‡

Data are mean ± SEM; n = 7.

HR = heart rate; MAP = mean aortic blood pressure; RPP = rate pressure product; LVSP and LVEDP = left ventricular systolic and end-diastolic pressure, respectively; DCBFV = diastolic coronary blood flow velocity; DCVR = diastolic coronary vascular resistance; EDL = end-diastolic segment length; EEVFL = end-early ventricular filling segment length; ESL = end-systolic segment length; SS = segment shortening; EVFF = early left ventricular filling fraction; L_w = preload recruitable stroke work length intercept; MAQ = mean aortic blood flow; SV = stroke volume; PWI = pressure work index.

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

† Significantly ($P < 0.05$) different from 25 $mg \cdot kg^{-1} \cdot h^{-1}$ propofol.

‡ Significantly ($P < 0.05$) different from 50 $mg \cdot kg^{-1} \cdot h^{-1}$ propofol.

decreases in mean arterial pressure, LV systolic and end-diastolic pressures, end-diastolic segment length, and end-systolic segment length ($P < 0.05$). Decreases in rate-pressure product, pressure-work index, and diastolic coronary vascular resistance were observed during infusion of the highest dose of propofol. Heart rate and diastolic coronary blood flow velocity were unchanged. Propofol caused dose-related reductions in M_W (67 ± 5 during control to 34 ± 4 mmHg during the 100 $mg \cdot kg^{-1} \cdot h^{-1}$ dose; fig. 1A), $+dP/dt_{max}$, and %SS in cardiomyopathic dogs, which is consistent with depression of intrinsic myocardial contractility. Propofol also caused dose-related decreases in mean aortic blood flow (2.14 ± 0.25 during control to 1.47 ± 0.17 l/min during the 100 $mg \cdot kg^{-1} \cdot h^{-1}$ dose; table 1) and stroke volume. The lowest dose of propofol caused a decrease in τ (62 ± 4 during control to 54 ± 4 ms; fig. 1B); however, no changes in τ were observed during administration of higher doses. Decreases in K (2.05 ± 0.54 during control to 0.33 ± 0.06 mm^{-1} during the 100 $mg \cdot kg^{-1} \cdot h^{-1}$ dose; fig. 1C) occurred concomitant with the declines in end-diastolic segment length and LV end-diastolic pressure. Propofol decreased dL/dt_E (57 ± 9 during control to 36 ± 7 mm/s during the 100 $mg \cdot kg^{-1} \cdot h^{-1}$ dose; fig. 2A) and TVI-E (4.8 ± 0.6 during control to 3.2 ± 0.5 mm during the 100 $mg \cdot kg^{-1} \cdot h^{-1}$ dose; fig. 3A), which is consistent with a reduction in the rate and extent of early LV filling. In contrast, dL/dt_A and TVI-A were unchanged (figs. 2B and 3B, respectively), and as a result, the ratios of dL/dt_E to dL/dt_A and TVI-E to TVI-A decreased (figs. 2C and 3C, respectively). Propofol also caused a reduction in early LV filling fraction (78.5 ± 3.0 during control to 67.9 ± 4.3% during the 50 $mg \cdot kg^{-1} \cdot h^{-1}$ dose; table 1). Propofol decreased R (3,850 ± 470 during control to 3,020 ± 270 $dyn \cdot s \cdot cm^{-5}$ during the 100 $mg \cdot kg^{-1} \cdot h^{-1}$ dose; fig. 4A) and increased C (0.70 ± 0.90 during control to 1.79 ± 0.23 ml/mmHg during the 100 $mg \cdot kg^{-1} \cdot h^{-1}$ dose; fig. 4B). Z_C remained unchanged during administration of propofol (fig. 4C).

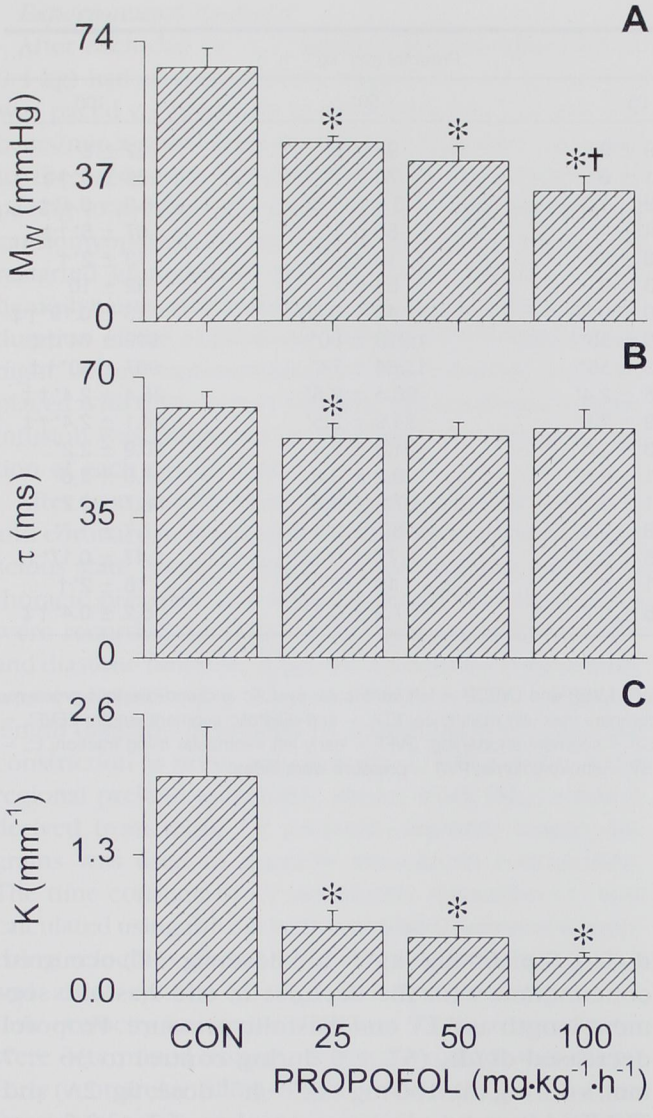

Fig. 1. Histograms illustrating the slope of the preload recruitable stroke work (M_W) relation *(A, top)*, the time constant of isovolumic relaxation (τ; *B, middle*), and the regional chamber stiffness (K; *C, bottom*) in the conscious state (CON) and during 25-, 50-, and 100-mg · kg^{-1} · h^{-1} infusions of propofol in dogs with pacing-induced cardiomyopathy. Data are mean ± SEM; n = 7. *Significantly different than CON ($P < 0.05$); †significantly different than 25 mg · kg^{-1} · h^{1} of propofol ($P < 0.05$).

Discussion

The current results indicate that 18 ± 3 days of rapid LV pacing produces cardiovascular effects that appear very similar to those we have reported previously in the identical canine model[23,24] When compared with the baseline systemic hemodynamics observed in healthy, chronically instrumented dogs,[3,12] conscious dogs with pacing-induced cardiomyopathy demonstrated increases in baseline heart rate (underlying sinus rhythm), LV end-diastolic pressure, end-diastolic segment length, and end-systolic segment length; decreases in mean arterial and LV systolic pressures; and LV systolic and diastolic dysfunction in the current and previous[23,24] studies. Cardiac output and systemic vascular resistance remained unchanged during pacing of this

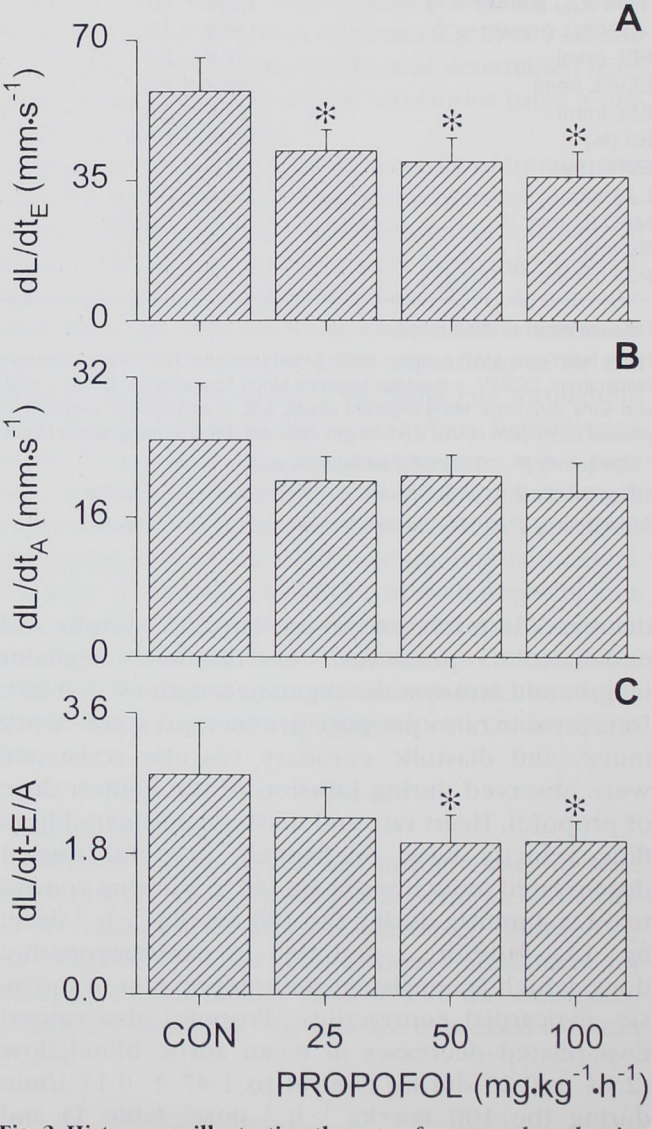

Fig. 2. Histograms illustrating the rate of segment lengthening during early LV filling (dL/dt_E; *A, top*) and atrial systole (dL/dt_A; *B, middle*) and the ratio of these parameters (dL/dt-E/A; *C, bottom*) in the conscious state (CON) and during 25-, 50-, and 100-mg · kg^{-1} · h^{-1} infusions of propofol in dogs with pacing-induced cardiomyopathy. Data are mean ± SEM; n = 7. *Significantly different than CON ($P < 0.05$).

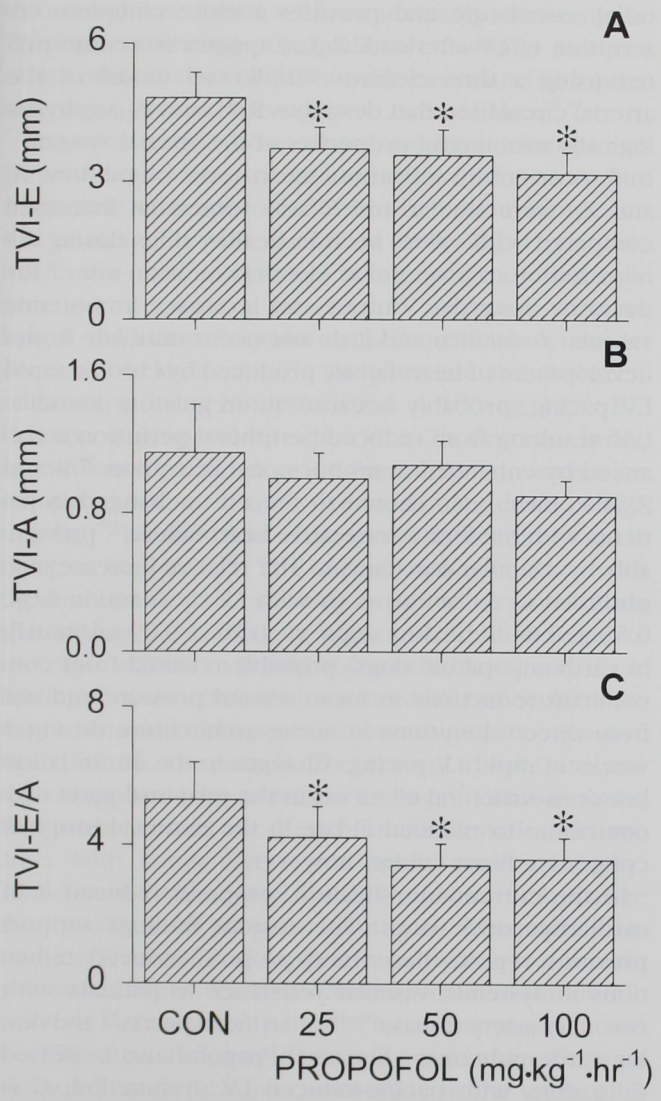

Fig. 3. Histograms illustrating the time–segment lengthening velocity integral during early LV filling (TVI-E; *A, top*) and atrial systole (TVI-A; *B, middle*) and the ratio of these parameters (TVI-E/A; *C, bottom*) in the conscious state (CON) and during 25-, 50-, and 100-mg · kg^{-1} · h^{-1} infusions of propofol in dogs with pacing-induced cardiomyopathy. Data are mean ± SEM; n = 7. *Significantly different than CON ($P < 0.05$).

duration. Thus, the current investigation examined the cardiovascular actions of propofol in a well-known, extensively characterized model of dilated cardiomyopathy[23–27] that has not decompensated into frank congestive heart failure.

These results in cardiomyopathic dogs indicate that propofol did not increase heart rate. These findings are similar to those observed in acutely instrumented dogs anesthetized with ketamine and fentanyl,[31] an experimental preparation characterized by pronounced depression of LV systolic and diastolic function.[32] The current results are also supported by previous studies[16–18] examining the cardiovascular effects of propofol anesthesia in patients with coronary artery disease and mildly depressed LV performance. In these studies, propofol did not change[17] or caused only modest increases in heart rate concomitant with a reduction in arterial pressure.[16,18] The lack of change in heart rate may re-

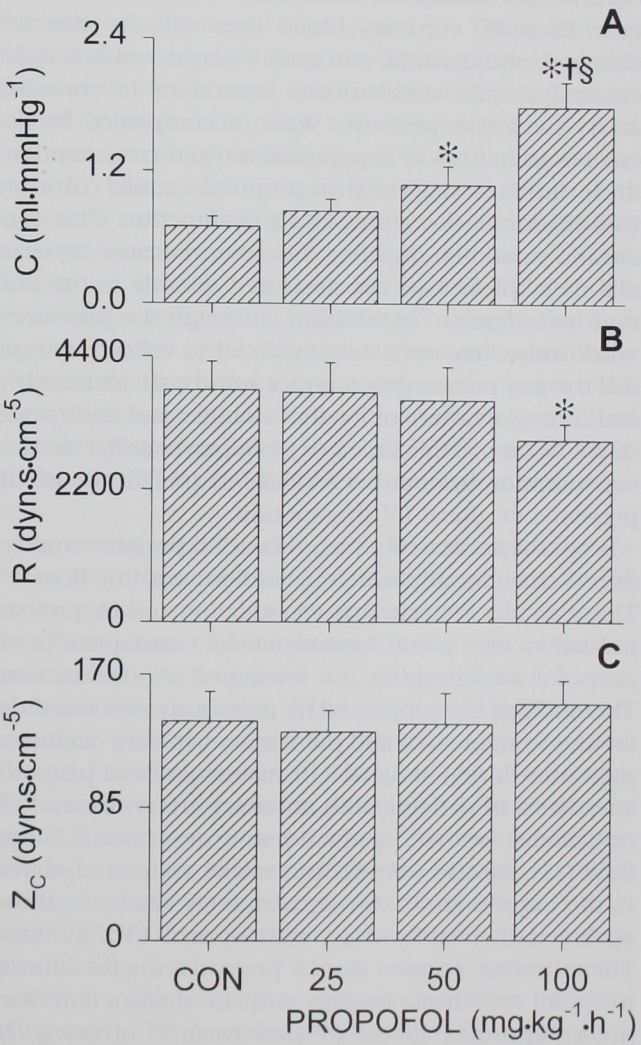

Fig. 4. Histograms illustrating total arterial compliance (C; *A, top*), total arterial resistance (R; *B, middle*), and characteristic aortic impedance (Z_C; *C, bottom*) in the conscious state (CON) and during 25-, 50-, and 100-mg · kg^{-1} · h^{-1} infusions of propofol in dogs with pacing-induced cardiomyopathy. Data are mean ± SEM; n = 7. *Significantly different than CON ($P < 0.05$); †significantly different than 25 mg · kg^{-1} · h^{-1} of propofol ($P < 0.05$); §significantly different than 50 mg · kg^{-1} · h^{-1} of propofol ($P < 0.05$).

flect altered baroreceptor reflex activity and downregulation of cardiac β_1-adrenoceptors concomitant with basal increases in central sympathetic nervous system tone and withdrawal of parasympathetic nervous system activity associated with the development of heart failure.[33]

Propofol also reduced calculated indices of myocardial oxygen consumption in dogs with pacing-induced LV dysfunction, results that may be attributed to favorable decreases in LV preload, afterload, and myocardial contractility during the maintenance of constant heart rate. Diastolic coronary blood flow velocity was unchanged, and diastolic coronary vascular resistance decreased despite simultaneous reductions in coronary artery perfusion pressure. When accompanied by decreases in indices of myocardial oxygen consumption, these findings suggest that propofol causes coronary vasodilation in the setting of LV dysfunction. This conclusion should be qualified, however, because myocardial metabolism was not measured directly in the current investigation. In addition, although the pressure-work index has been demonstrated to reflect myocardial oxygen consumption under anesthesia accurately[34] and during a variety of loading changes and contractile states *in vivo,*[35] this index of global myocardial oxygen consumption has not been validated specifically in the presence of global LV dysfunction.

Propofol decreased LV end-diastolic pressure and reduced chamber dimension in cardiomyopathic dogs.[3,12] These results indicate that venodilation and LV preload reduction are major hemodynamic consequences of propofol anesthesia in the setting of LV dysfunction. The findings are supported by previously described decreases in right atrial and pulmonary capillary occlusion pressures during induction or maintenance of propofol anesthesia in patients with coronary artery disease[16-18] or artificial hearts.[36] Reductions in mean aortic blood flow (*i.e.,* cardiac output) and stroke volume observed in the current study were qualitatively similar to those observed in healthy dogs with normal LV function.[3] These findings suggest that LV preload reduction during propofol anesthesia in dogs with LV dysfunction does not compromise global LV performance adversely. In fact, the decreases in cardiac dimension and chamber pressures in diastole may be beneficial.

The effects of chronic LV pacing and propofol anesthesia on LV afterload in cardiomyopathic dogs were quantified with $Z_{in}(\omega)$ spectra. In contrast to calculated systemic vascular resistance, $Z_{in}(\omega)$ incorporates the frequency-dependent and viscoelastic properties of the arterial vasculature and provides a more complete description of LV afterload. $Z_{in}(\omega)$ spectra were interpreted using a three-element Windkessel model of the arterial circulation that describes R, C, and Z_C as physiologically meaningful properties of the arterial system.[37] In the current investigation, mean aortic blood flow, R, and Z_C were similar and C was somewhat increased compared with values seen in healthy dogs during administration of propofol at identical infusion rates.[3] Reductions in cardiac output and increases in systemic vascular resistance and R do not occur until late in the development of heart failure produced by chronic rapid LV pacing, probably because autoregulatory vasodilation resulting from reduced peripheral perfusion is balanced by enhanced neurohormonal activation.[38] R and Z_C also have been shown to remain unchanged in patients with moderate congestive heart failure,[39] presumably by a similar mechanism. The relative increase in C observed in conscious dogs with LV dysfunction (*e.g.,* 0.53 ± 0.04 in healthy dogs[3] vs. 0.70 ± 0.09 ml/mmHg in cardiomyopathic dogs) probably resulted from concomitant reductions in mean arterial pressure and not from direct alterations in aortic architecture during 3 weeks of rapid LV pacing. Changes in the interrelation between structural elements in the proximal aorta may contribute to reduced C late in the natural history of congestive heart failure, however.[40]

In the current investigation, propofol reduced R in cardiomyopathic dogs. The current findings support previous reports describing propofol-induced reductions in systemic vascular resistance in patients with coronary artery disease[16-18] or artificial hearts[36] and during cardiopulmonary bypass.[41] Propofol also increased C in dogs with pacing-induced LV dysfunction. C is determined primarily by aortic compliance,[42] and these elastic properties of the proximal aorta allow it to efficiently store and redistribute LV ejection energy during systole and diastole, respectively. The magnitude of the alterations in R and C produced by propofol was similar in cardiomyopathic compared with healthy dogs[3]; however, propofol did not increase Z_C in dogs with pacing-induced LV dysfunction. Although the resistance of the aorta to LV ejection makes a relatively small contribution to R, an increase in Z_C, such as that observed with propofol in healthy dogs,[3] may contribute to an attenuation of LV-arterial coupling and mechanical efficiency.[43] Thus, the current findings suggest that propofol produces beneficial decreases in resistance to LV ejection in the presence of LV dysfunction by favorably affecting the mechanical properties of the aorta and

the arterial vasculature without adversely increasing Z_C. The current findings are qualitatively similar to those observed with the arterial vasodilator sodium nitroprusside in patients with congestive heart failure.[39,44]

Propofol caused dose-related negative inotropic effects in dogs with pacing-induced LV dysfunction. The magnitude of propofol-induced depression of myocardial contractility was quantified with M_W, a relatively heart rate- and load-independent index of inotropic state derived from a series of LV pressure-segment length diagrams. Propofol caused qualitatively similar decreases in M_W in dogs in the presence and absence[12] of pacing-induced LV dysfunction. A 100-mg $\cdot$ kg^{-1} $\cdot$ h^{-1} infusion of propofol caused a 51 $\pm$ 7% decrease in M_W in cardiomyopathic dogs in the current investigation compared with a 50 $\pm$ 6% decrease in M_W during a 120-mg $\cdot$ kg^{-1} $\cdot$ h^{-1} infusion of propofol in healthy dogs in our previous study.[12] The current results contrast with the findings of a recent study *in vitro*[20] demonstrating that propofol causes more pronounced direct negative inotropic effects in failing myocardia; however, these findings[20] were obtained in isolated LV trabecular myocardia obtained from pigs with overt signs of congestive heart failure. Conversely, the current results are partially supported by previous findings[22] demonstrating that propofol does not alter contractile function in hamsters with congenital hypertrophic cardiomyopathy. The data of Hebbar *et al.*[20] and Riou *et al.*[22] emphasize that the effects of propofol on intrinsic myocardial contractility in models of cardiomyopathy *in vitro* remain somewhat controversial. Differences in basal autonomic nervous system activity between cardiomyopathic and healthy dogs also may have influenced the effects of propofol on myocardial contractility in the current investigation and cannot be completely excluded from the analysis. The mechanisms responsible for the negative inotropic effects of propofol in the failing heart are unknown. It is likely that the inhibition of transsarcolemmal calcium current[45] and L-type calcium channel function[46] observed with propofol in normal cardiac muscle also may play key roles in the contractile depression observed in the current and previous investigations.[20,21] These hypotheses remain to be tested *in vitro,* however.

The 25-mg $\cdot$ kg^{-1} $\cdot$ h^{-1} dose of propofol decreased τ in dogs with pacing-induced LV dysfunction despite a concomitant reduction in contractility. This result probably occurred as a consequence of decreases in end-diastolic segment length and LV end-diastolic pressure because relaxation of cardiac muscle has been shown to be preload dependent.[47] In contrast to the findings with the lowest dose, the 50- and 100-mg $\cdot$ kg^{-1} $\cdot$ h^{-1} doses of propofol did not change τ. Further reductions in LV preload and decreases in afterload observed with higher doses of this intravenous anesthetic were balanced by negative inotropic effects. Despite the modest improvement in τ observed with the 25-mg $\cdot$ kg^{-1} $\cdot$ h^{-1} dose of propofol, indices of the rate and extent of early LV filling (*e.g.,* dL/dt_E and TVI-E) decreased. In addition, propofol caused declines in early LV filling fraction and the dL/dt-E/A and TVI-E/A ratios because dL/dt_A and TVI-A remained unchanged (figs. 2 and 3). These findings suggest that early LV filling may be compromised and the contribution of atrial systole to total LV filling accentuated by propofol in dogs with cardiomyopathy. The rate and extent of cardiac muscle lengthening during rapid LV filling, however, are also directly affected by several factors, including LV loading conditions, the left atrial-LV pressure gradient, and inotropic state.[48] Venodilators are known to reduce dL/dt_E and TVI-E by decreasing the left atrial-LV gradient.[48] Despite the finding that the left atrial-LV gradient was not specifically quantified in the current investigation, it appears to be likely that propofol-induced reductions in LV preload probably played an important role in the reduction in dL/dt_E and TVI-E produced by this intravenous anesthetic.

The current results with propofol are somewhat different than those obtained with isoflurane in a similar experimental model of pacing-induced LV dysfunction.[49] Isoflurane (1.1 minimum alveolar concentration) increased TVI-E/A and did not reduce dL/dt-E/A, suggesting an improvement in the pattern of LV filling concomitant with reductions in chamber dimension and LV end-diastolic pressure.[49] The previous results with isoflurane were obtained in dogs after only 10 days of rapid LV pacing, an experimental preparation characterized by decreases in the contribution of early LV filling and reductions in or reversal of the classical E to A ratio.[27] The current investigation was conducted in dogs after almost 3 weeks of pacing, during experimental conditions that display normalization of the early LV filling rate as LV compliance decreases. Thus, the influence of propofol on indices of LV filling was examined in a model with a greater severity of LV dysfunction than those encountered in our previous study with volatile anesthetics.[49] Decreases in K produced by propofol were accompanied by declines in LV end-diastolic pressure and chamber dimension. These findings indicate that propofol-induced venodilation caused the LV pres-

sure-segment length diagram to shift to the left, causing the left ventricle to operate in a more compliant region of the end-diastolic pressure-length relation in propofol-anesthetized compared with conscious, cardiomyopathic dogs. Interpretation of these results require qualification, however, because the pericardium remained open after the surgical implantation of instruments and during the development of pacing-induced cardiomyopathy.

We[3,12] have previously demonstrated that the doses of propofol used in the current investigation produce reliable anesthesia in chronically instrumented dogs. Although plasma concentrations of propofol were not measured in this investigation, a previous study[50] demonstrated that infusions of 20 and 40 $mg \cdot kg^{-1} \cdot h^{-1}$ produced plasma concentrations of 2-13 $\mu g/ml$ in dogs. These plasma concentrations lie within the anesthetic range in humans. Thus, the 25- and 50-$mg \cdot kg^{-1} \cdot h^{-1}$ infusions of propofol used in the current investigation may correlate with clinically relevant propofol concentrations. Direct comparison of the cardiovascular effects of this intravenous anesthetic between dogs with pacing-induced cardiomyopathy and humans with heart failure should be made with caution, however.

In summary, the current results indicate that propofol produces favorable reductions in LV preload, afterload, and K and preserves LV relaxation but also causes negative inotropic effects and impairs LV filling dynamics in dogs with dilated cardiomyopathy by chronic rapid LV pacing.

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