

# Alteration of Canine Left Ventricular Diastolic Function by Intravenous Anesthetics In Vivo

## Ketamine and Propofol

Paul S. Pagel, M.D.,\* William T. Schmeling, M.D., Ph.D.,†  
John P. Kampine, M.D., Ph.D.,‡ David C. Warltier, M.D., Ph.D.§

Diastolic function has been shown to influence overall cardiac performance significantly, but the effect of intravenous anesthetics on diastolic function has not been previously characterized *in vivo*. The effects of ketamine and propofol on two indices of left ventricular diastolic function were examined in chronically instrumented dogs. Because autonomic nervous system function may significantly influence the systemic hemodynamic actions produced by intravenous anesthetics *in vivo*, experiments were performed in the presence of pharmacologic blockade of the autonomic nervous system. Two groups comprising a total of 14 experiments were performed using 7 dogs instrumented for measurement of aortic and left ventricular pressure, the maximum rate of increase of left ventricular pressure (dP/dt), subendocardial segment length, and cardiac output. Systemic hemodynamics and diastolic function were recorded and evaluated in the conscious state and after a 20-min equilibration at 25-, 50-, and 100-mg · kg<sup>-1</sup> · h<sup>-1</sup> infusion doses of ketamine or propofol. Ventricular relaxation was described using the time constant of isovolumetric relaxation ( $\tau$ ) assuming a nonzero asymptote of ventricular pressure decay. Regional chamber stiffness, an index of passive ventricular filling, was described using an exponential equation relating segment length to ventricular pressure between minimum ventricular pressure and the onset of atrial systole. Ketamine produced a significant ( $P < 0.05$ ) and dose-dependent increase in the time constant of isovolumetric relaxation ( $\tau$ , 32.8 ± 2.8 during control to 53.3 ± 4.2 ms<sup>-1</sup> at 100 mg · kg<sup>-1</sup> · h<sup>-1</sup>). Ketamine also caused an increase in regional passive chamber stiffness ( $K_p$ , 0.37 ± 0.03 during control to 0.69 ± 0.09 mm<sup>-1</sup> at 100 mg · kg<sup>-1</sup> · h<sup>-1</sup>) in a dose-dependent fashion indicating a decrease in ventricular compliance. Neither isovolumetric relaxation nor regional chamber stiffness changed significantly with propofol. Although the effects of the intravenous anesthetics on systolic function represent a confounding variable that could not be completely excluded from the analysis of the data, the results indicate that ketamine impairs left ventricular diastolic function in the chronically instrumented dog with autonomic nervous system blockade. In contrast, propofol does not appear to alter

diastolic function even though it produces a similar hemodynamic profile with the doses administered in this investigation. (Key words: Anesthetics, intravenous: ketamine; propofol. Heart: diastole; diastolic left ventricular function; isovolumetric relaxation; myocardial function; ventricular compliance.)

FUNCTION OF THE LEFT VENTRICLE during diastole has attracted considerable recent attention because diastolic mechanics significantly affect overall cardiac performance. Although clinical congestive heart failure most often occurs as a consequence of compromised systolic function, this syndrome may also occur in certain patients with abnormalities of diastolic function in the absence of significant alterations in systolic performance.<sup>1-4</sup> Study of the action of anesthetics on diastolic function is important because anesthetics may alter the rate and extent of ventricular filling, factors that play a critical role in the mechanical efficiency of the heart. For example, potent inhalational anesthetics have been shown to prolong isovolumetric relaxation<sup>5,6</sup> and may also impair passive ventricular compliance.<sup>6</sup> These alterations could significantly contribute to depressed cardiac performance observed with the volatile anesthetic agents. Several investigators working *in vitro*<sup>7-10</sup> have postulated that ketamine may alter myocardial relaxation; however, the action of this commonly used intravenous anesthetic on diastolic function *in vivo* has not been previously characterized. Similarly, although the effects of propofol on systemic hemodynamics<sup>11-13</sup> and left ventricular systolic function<sup>14-17</sup> have been described, the effects of this new intravenous agent on diastolic function are also unknown.

The present investigation was undertaken to examine systematically the effects of ketamine and propofol on active (isovolumetric relaxation) and passive (regional chamber stiffness) components of left ventricular diastolic function in the chronically instrumented dog. Experiments were performed in the presence of autonomic nervous system blockade because both ketamine and propofol have been shown to alter autonomic nervous system function variably and to produce indirect effects on systemic hemodynamics mediated *via* an intact autonomic nervous

\* Fellow in Anesthesiology.

† Associate Professor of Anesthesiology and Pharmacology.

‡ Professor and Chairman of Anesthesiology.

§ Professor of Anesthesiology, Pharmacology, and Medicine (Division of Cardiology), and Vice Chairman for Research, Department of Anesthesiology.

Received from the Departments of Anesthesiology, Pharmacology, and Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin and the Zablocki Veterans Administration Medical Center, Milwaukee, Wisconsin. Accepted for publication November 4, 1991. Supported by United States Public Health Service grants HL 36144 and HL 32911, Anesthesiology Research Training Grant GM 08377, and Veterans Administration Medical Research Funds.

Address reprint requests to Dr. Warltier: Medical College of Wisconsin, MFRC, Room A1000, 8701 West Watertown Plank Road, Milwaukee, Wisconsin 53226.

‡ Department of Health, Education, and Welfare (Department of Health and Human Services): Publication no. (NIH) 85-23. Revised 1985.

system.<sup>18-22</sup> Therefore, the direct actions of ketamine and propofol on isovolumetric relaxation and regional chamber stiffness were evaluated independent of autonomic nervous system reflexes.

### Materials and Methods

All experimental procedures and protocols used in this investigation were reviewed and approved by the Animal Care Committee of the Medical College of Wisconsin. Furthermore, all conformed to the Guiding Principles in the Care and Use of Animals of the American Physiologic Society and were in accordance with the Guide for the Care and Use of Laboratory Animals.

#### IMPLANTATION OF INSTRUMENTS

Surgical implantation of instruments has been previously described in detail.<sup>6</sup> Briefly, conditioned mongrel dogs weighing between 20 and 30 kg were fasted overnight and anesthetized with sodium thiamylal (10 mg · kg<sup>-1</sup>). Following tracheal intubation, anesthesia was maintained with enflurane (2.0–3.0%) in 100% oxygen (1 l · min<sup>-1</sup>) via positive pressure ventilation. A thoracotomy was performed under sterile conditions in the left fifth intercostal space. Heparin-filled catheters were placed in the descending thoracic aorta and the right atrium for measurement of aortic blood pressure and fluid or drug administration, respectively. An ultrasonic flow probe (Transonics, Ithaca, NY) was positioned around the ascending thoracic aorta for measurement of relative cardiac output. A pair of miniature ultrasonic segment length transducers (5 MHz) for measurement of changes in regional contractile function (segment shortening) were implanted within the left ventricular subendocardium. A high-fidelity, miniature micromanometer (P7, Konigsberg Instruments, Pasadena, CA) was implanted in the left ventricle for measurement of left ventricular pressure and of the maximum rate of increase of left ventricular pressure (dP/dt<sub>max</sub>). A heparin-filled catheter was inserted into the left atrial appendage, and the left ventricular micromanometer was cross-calibrated *in vivo* against pressures measured via arterial and left atrial catheters (Gould P<sub>50</sub> pressure transducer, Oxnard, CA). A precalibrated Doppler ultrasonic flow transducer (20 MHz) was placed around the proximal left anterior descending coronary artery for measurement of diastolic coronary blood flow velocity. All instrumentation was secured, tunneled between the scapulae, and exteriorized via several small incisions. The pericardium was left widely open, the chest wall closed in layers, and the pneumothorax evacuated by a chest tube left *in situ*. Each dog was fitted with a jacket (Alice King Chatham, Los Angeles, CA) to prevent damage to the instruments and catheters, which were housed in an aluminum box within the jacket pocket.

After surgery, each dog was treated with analgesics (buprenorphine 0.02 mg/kg). Antibiotic prophylaxis consisted of procaine penicillin G (25,000 U/kg) and gentamicin (4.5 mg/kg). The chest tube was removed on the first postoperative day, and dogs were allowed to recover for a minimum of 10 days prior to experimentation. Dogs were trained to stand quietly in a sling during hemodynamic monitoring in the postoperative period. Segment length signals were driven and monitored by ultrasonic amplifiers (Hartley, Houston, TX). End systolic segment length was determined at maximum negative left ventricular dP/dt, and end diastolic segment length was determined at the onset of left ventricular isovolumetric contraction. The lengths were normalized according to the method described by Theroux *et al.*<sup>23</sup> Percent segment shortening (%SS) was calculated by use of the equation: %SS = (EDL – ESL) × 100/EDL, where EDL = end-diastolic segment length and ESL = end-systolic segment length. Diastolic coronary vascular resistance was calculated as the quotient of diastolic arterial pressure and diastolic coronary blood flow velocity (Hz × 10<sup>2</sup>). All hemodynamic data were continuously recorded on a Hewlett Packard 7758A polygraph (Hewlett Packard, San Francisco, CA) and digitized via a computer interfaced with an analog-to-digital converter.

#### EXPERIMENTAL PROTOCOL

Dogs (n = 7) were assigned to receive either ketamine or propofol in a random fashion on separate days. All dogs were fasted overnight, and fluid deficits were replaced before experimentation with crystalloid (500 ml lactated Ringer's solution). After instrumentation was calibrated and baseline hemodynamic data recorded, the autonomic nervous system was pharmacologically blocked with intravenous propranolol (2 mg · kg<sup>-1</sup>), atropine methylnitrate (3 mg · kg<sup>-1</sup>), and hexamethonium (20 mg · kg<sup>-1</sup>). Blockade of the autonomic nervous system was instituted to prevent reflex changes in systemic hemodynamics produced by ketamine or propofol.

After control hemodynamics had been recorded in the conscious, autonomically blocked state, continuous left ventricular pressure and segment length waveforms (20–25 cardiac cycles) were recorded on a digital storage oscilloscope (Nicolet Model 4094, Madison, WI) for later off-line analysis of isovolumetric relaxation and regional chamber stiffness. Anesthesia was then induced with ketamine or propofol in a random fashion by intravenous bolus (10 mg · kg<sup>-1</sup>) injection. After tracheal intubation, anesthesia was maintained with ketamine or propofol via a continuous infusion at 25, 50, or 100 mg · kg<sup>-1</sup> · h<sup>-1</sup> in a random order. Each dog's lungs were mechanically ventilated with a nitrogen (79%) and oxygen (21%) mixture at a constant flow rate of 2 l · min<sup>-1</sup>. Hemodynamics were

recorded and ventricular pressure and segment length waveforms were obtained in a manner described above after 20 min of equilibration at each dose of intravenous anesthetic. The anesthetic concentration was then changed, and measurements were repeated after similar equilibration. Arterial blood gases were maintained at conscious levels by adjustment of nitrogen and oxygen concentrations during each experiment.

At the completion of all experiments, anesthesia was discontinued and emergence allowed to occur. Three days were allowed between experiments for complete recovery from autonomic nervous system blockade and anesthesia. A total of 14 experiments in two separate groups (ketamine or propofol) were completed in which the same seven dogs were used.

Each of the two phases of diastole, isovolumetric relaxation and regional wall stiffness, was analyzed off-line. Isovolumetric relaxation was described assuming a nonzero asymptote of ventricular pressure decline using the method of Thompson *et al*<sup>24</sup> and the modification of Raff and Glantz.<sup>25</sup> Left ventricular pressure between maximum negative  $dP/dt$  and 5 mmHg above end-diastolic pressure (physiologically associated with the opening of the mitral valve) *versus* time data in 2-ms intervals were fitted to a three-constant exponential equation:

$$P = ae^{-t/\tau} + c \quad (1)$$

where  $c$  = the true asymptote to which pressure declines;  $a + c$  = ventricular pressure at peak negative  $dP/dt$ ; and  $\tau$  = the rate of relaxation ( $\text{ms}^{-1}$ ) assuming a nonzero asymptote. It can be easily shown<sup>25</sup> that

$$\frac{dP}{dt} = \frac{c}{\tau} - \frac{P}{\tau} \quad (2)$$

Therefore, a plot of  $dP/dt$  against ventricular pressure between peak negative  $dP/dt$  and 5 mmHg above end-diastolic pressure yields the nonzero asymptotic isovolumetric time constant ( $\tau$ ) as the negative inverse of the slope.

Regional chamber stiffness, a regional indicator of ventricular compliance during passive filling, was derived from ventricular pressure-segment length data as previously described.<sup>6,26</sup> Beginning at minimum pressure, ventricular pressure was plotted against corresponding segment length at 2-ms intervals until the onset of atrial systole (incorporating both rapid and slow ventricular filling) had been reached. A least squares regression analysis was used to describe a monoexponential relationship between pressure and segment length:

$$P = De^{K_p \cdot L} \quad (3)$$

where  $P$  = left ventricular pressure;  $L$  = corresponding segment length;  $D$  = a derived constant; and  $K_p$  = the regional chamber stiffness constant.

## STATISTICAL ANALYSIS

Statistical analysis of data within each group during the conscious state with and without autonomic nervous system blockade and during all anesthetic interventions was performed by analysis of variance with repeated measures followed by application of the Student's  $t$  test with Bonferroni's correction. Changes within each group were considered statistically significant when the probability ( $P$ ) value was  $< 0.05$ . Least squares regression analysis was used to characterize the exponential relationship between ventricular pressure and segment length (calculation of  $K_p$ ). The relationship between  $dP/dt$  and ventricular pressure used to calculate the time constant of isovolumetric relaxation was described using a linear regression analysis. All data were expressed as mean  $\pm$  SEM.

## Results

Autonomic nervous system blockade produced a significant ( $P < 0.05$ ) increase in heart rate and decreases in mean arterial pressure, left ventricular systolic pressure,  $dP/dt_{\max}$ , diastolic coronary vascular resistance, systemic vascular resistance, and stroke volume. No changes in left ventricular end-diastolic pressure, rate-pressure product, diastolic coronary blood flow velocity, cardiac output, or percent segment shortening were observed (tables 1 and 2). Regression coefficients ( $r^2$ ) obtained in the calculation of  $\tau$  and  $K_p$  were  $\geq 0.98$  and  $\geq 0.94$ , respectively.

In the presence of autonomic nervous blockade, ketamine produced significant ( $P < 0.05$ ) decreases in heart rate and rate-pressure product (table 1). Increases in left ventricular end-diastolic pressure ( $8 \pm 1$  during control to  $13 \pm 2$  mmHg at  $100\text{-mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  dose) and systemic vascular resistance ( $2,000 \pm 270$  during control to  $3,340 \pm 340$   $\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}$  at  $100\text{-mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  dose) were noted with ketamine. Ketamine also caused dose-dependent decreases in cardiac output ( $2.9 \pm 0.2$  during control to  $1.7 \pm 0.2$   $\text{l} \cdot \text{min}^{-1}$  at the high dose). No changes in mean arterial pressure, left ventricular systolic pressure, diastolic coronary blood flow velocity, or diastolic coronary vascular resistance were observed during ketamine anesthesia.

Ketamine produced significant ( $P < 0.05$ ) and dose-dependent decreases in global myocardial contractility as assessed by  $dP/dt_{\max}$  ( $1,830 \pm 180$  during control to  $850 \pm 80$   $\text{mmHg} \cdot \text{s}^{-1}$  at  $100\text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ), consistent with a direct myocardial depressant effect independent of the autonomic nervous system. Dose-related decreases in inotropic state were also identified by percent segment shortening ( $15.7 \pm 2.0$  during control to  $7.1 \pm 0.8\%$  at  $100\text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ). The time constant of isovolumetric relaxation increased in a significant and dose-dependent fashion during administration of ketamine (fig. 1;  $33 \pm 3$  during control to  $53 \pm 4$  ms at  $100\text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ), indicating a direct prolongation of this phase of diastole. In

TABLE 1. Systemic and Coronary Hemodynamic Effects of Ketamine

	Conscious Pre-ANS Block	Conscious ANS Block	Ketamine Dose (mg · kg <sup>-1</sup> · h <sup>-1</sup> )		
			25	50	100
HR (beats · min <sup>-1</sup> )	84 ± 4*	114 ± 5	105 ± 6	103 ± 6*	98 ± 6*
MAP (mmHg)	109 ± 3*	74 ± 7	74 ± 7	72 ± 8	66 ± 6
RPP (beats · min <sup>-1</sup> · mmHg · 10 <sup>3</sup> )	11.6 ± 0.5	10.6 ± 0.9	9.5 ± 1.0	9.2 ± 1.0	7.8 ± 0.8*
LVSP (mmHg)	139 ± 3*	99 ± 6	97 ± 7	96 ± 8	88 ± 5
LVEDP (mmHg)	10 ± 1	8 ± 1	10 ± 1	11 ± 1	13 ± 2*
dP/dt <sub>max</sub> (mmHg · s <sup>-1</sup> )	2830 ± 130*	1830 ± 180	1390 ± 110*	1210 ± 110*	850 ± 80*†
DCBFV (Hz · 10 <sup>3</sup> )	40.4 ± 4.4	38.0 ± 5.6	35.3 ± 6.0	35.8 ± 5.8	37.2 ± 6.4
DCVR (ru)	2.56 ± 0.29*	1.84 ± 0.38	2.04 ± 0.41	2.01 ± 0.44	1.86 ± 0.45
CO (l · min <sup>-1</sup> )	2.8 ± 0.2	2.9 ± 0.2	2.2 ± 0.2*	2.0 ± 0.2*	1.7 ± 0.2*†
SVR (dyn · s · cm <sup>-5</sup> )	3270 ± 270*	2000 ± 270	2700 ± 270	3070 ± 270*	3340 ± 340*
SV (ml)	33 ± 2*	26 ± 2	21 ± 1*	19 ± 2*	17 ± 2*
SS (%)	15.7 ± 1.7	15.7 ± 2.0	12.3 ± 1.3	10.0 ± 0.7*	7.1 ± 0.8*†

All data are mean ± SEM; n = 7.

ANS = autonomic nervous system; HR = heart rate; MAP = mean arterial pressure; RPP = rate pressure product; LVSP = left ventricular systolic pressure; LVEDP = left ventricular end diastolic pressure; DCBFV = diastolic coronary blood flow velocity; DCVR = diastolic

coronary vascular resistance; CO = cardiac output; SVR = systemic vascular resistance; SV = stroke volume; SS = segment shortening.

\* Significantly ( $P < 0.05$ ) different from conscious, autonomically blocked state.

† Significantly ( $P < 0.05$ ) different from 25-mg · kg<sup>-1</sup> · h<sup>-1</sup> dose.

addition, administration of ketamine caused increases in regional chamber stiffness (fig. 2;  $0.37 \pm 0.03$  during control to  $0.69 \pm 0.09$  mm<sup>-1</sup> at 100 mg · kg<sup>-1</sup> · h<sup>-1</sup>), indicating a significant decrease in passive ventricular compliance.

In the presence of autonomic nervous system blockade, propofol produced hemodynamic effects (table 2) that were similar to those produced by ketamine. Propofol decreased heart rate, mean arterial pressure, left ventricular systolic pressure, and rate-pressure product primarily at the 100-mg · kg<sup>-1</sup> · h<sup>-1</sup> dose (table 2). Cardiac output decreased ( $2.7 \pm 0.2$  during control to  $2.1 \pm 0.2$  l · min<sup>-1</sup> at 25 mg · kg<sup>-1</sup> · h<sup>-1</sup>), but this decline was not dose-de-

pendent. No significant changes in left ventricular end-diastolic pressure, diastolic coronary blood flow velocity, diastolic coronary vascular resistance, or systemic vascular resistance were observed. Propofol produced a significant ( $P < 0.05$ ) reduction in left ventricular dP/dt<sub>max</sub> ( $1,830 \pm 120$  during control to  $1,390 \pm 130$  mmHg · s<sup>-1</sup> at 100 mg · kg<sup>-1</sup> · h<sup>-1</sup>), consistent with a negative inotropic effect. Regional myocardial contractility, as assessed by percent segment shortening, also decreased with propofol ( $17.0 \pm 1.9$  during control to  $14.6 \pm 1.6\%$  at 100 mg · kg<sup>-1</sup> · h<sup>-1</sup>). No changes in the time constants of isovolumetric relaxation or regional chamber stiffness were observed with any dose of propofol (figs. 1 and 2).

TABLE 2. Systemic and Coronary Hemodynamic Effects of Propofol

	Conscious Pre-ANS Block	Conscious ANS Block	Propofol Dose (mg · kg <sup>-1</sup> · h <sup>-1</sup> )		
			25	50	100
HR (beats · min <sup>-1</sup> )	83 ± 5*	113 ± 5	105 ± 6	102 ± 6	99 ± 5*
MAP (mmHg)	99 ± 5*	74 ± 4	70 ± 7	66 ± 6	59 ± 6*
RPP (beats · min <sup>-1</sup> · mmHg · 10 <sup>3</sup> )	10.3 ± 0.4	10.4 ± 0.8	9.7 ± 1.2	8.7 ± 1.0	7.8 ± 0.9*
LVSP (mmHg)	129 ± 5*	95 ± 4	93 ± 6	87 ± 5	82 ± 6*
LVEDP (mmHg)	10 ± 1	7 ± 2	8 ± 1	8 ± 1	9 ± 2
dP/dt <sub>max</sub> (mmHg · s <sup>-1</sup> )	2610 ± 130*	1830 ± 120	1650 ± 120	1550 ± 135*	1390 ± 130*†
DCBFV (Hz · 10 <sup>3</sup> )	39.3 ± 7.6	46.6 ± 8.0	43.8 ± 9.0	46.3 ± 10.6	43.1 ± 9.7
DCVR (ru)	2.43 ± 0.51*	1.51 ± 0.45	1.46 ± 0.20	1.28 ± 0.16	1.16 ± 0.12
CO (l · min <sup>-1</sup> )	2.6 ± 0.3	2.7 ± 0.2	2.1 ± 0.2*	2.1 ± 0.2*	2.0 ± 0.2*
SVR (dyn · s · cm <sup>-5</sup> )	3190 ± 300*	2180 ± 240	2820 ± 330	2590 ± 250	2340 ± 250
SV (ml)	32 ± 4*	24 ± 2	20 ± 2	20 ± 1	21 ± 1
SS (%)	17.0 ± 1.6	17.0 ± 1.9	15.4 ± 1.4	15.0 ± 1.5*	14.6 ± 1.6*

All data are mean ± SEM; n = 7.

ANS = autonomic nervous system; HR = heart rate; MAP = mean arterial pressure; RPP = rate pressure product; LVSP = left ventricular systolic pressure; LVEDP = left ventricular end diastolic pressure; DCBFV = diastolic coronary blood flow velocity; DCVR = diastolic

coronary vascular resistance; CO = cardiac output; SVR = systemic vascular resistance; SV = stroke volume; SS = segment shortening.

\* Significantly ( $P < 0.05$ ) different from conscious, autonomically blocked state.

† Significantly ( $P < 0.05$ ) different from 25-mg · kg<sup>-1</sup> · h<sup>-1</sup> dose.

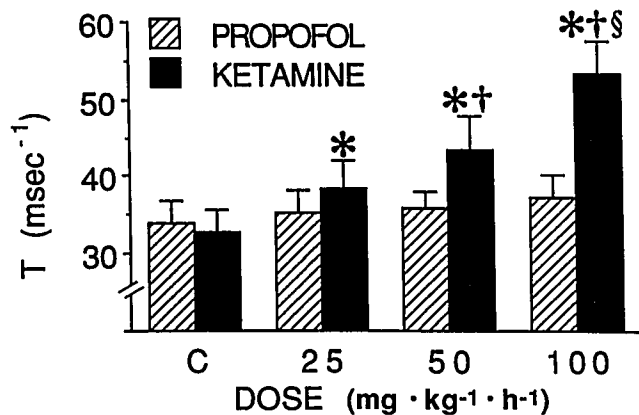


FIG. 1. Effects of ketamine and propofol on the time constant of isovolumetric relaxation (T). \*Significantly ( $P < 0.05$ ) different from the autonomically blocked, conscious control (C). †Significantly ( $P < 0.05$ ) different from the 25-mg · kg<sup>-1</sup> · h<sup>-1</sup> dose. §Significantly ( $P < 0.05$ ) different from the 50-mg · kg<sup>-1</sup> · h<sup>-1</sup> dose.

### Discussion

Ketamine has achieved popularity as an intravenous induction agent in certain patients with hemodynamic compromise. The clinical recognition that the use of ketamine can also lead to acute cardiovascular decompensation in a subset of critically ill patients has stimulated intense study aimed at understanding the direct effects of ketamine on myocardial function. The effects of ketamine on systemic hemodynamics have been extensively described. Ketamine produces dramatic increases in heart rate and arterial pressure, which have been attributed to the central and peripheral sympathomimetic actions of this drug.<sup>18</sup> On a cellular level, ketamine has been shown to block reuptake of monoamines including norepinephrine in adrenergic nerves, a mechanism of action similar to that of cocaine.<sup>20,21</sup> In the presence of an impaired sympathetic nervous system, ketamine has also been described to produce direct myocardial depressant effects *in vivo*<sup>27,28</sup> and *in vitro*.<sup>8-10,29</sup> However, this conclusion remains controversial, as some investigations *in vitro*<sup>7,30</sup> have offered evidence that ketamine may, in fact, produce direct myocardial stimulation independent of the actions of this agent on autonomic nervous system function.

The effects of ketamine on left ventricular diastolic function have not been described *in vivo*. Examination of the effect of anesthetics on this phase of the cardiac cycle is important because alteration of the rate and extent of ventricular filling produced by anesthetic agents may significantly influence overall cardiac function. Four studies completed *in vitro*<sup>7-10</sup> have suggested that ketamine may alter ventricular relaxation. Rusy *et al.*<sup>8</sup> demonstrated that ketamine depressed contractile function in rabbit papillary muscle *via* inhibition of transsarcolemmal calcium currents. Since ventricular relaxation is an active, energy-

dependent process resulting from dissociation of actin-myosin linkages by reuptake of cytoplasmic calcium into the sarcoplasmic reticulum, alteration in transsarcolemmal calcium kinetics demonstrated by these authors<sup>8</sup> may offer a potential mechanism by which ketamine impairs ventricular relaxation. Similarly, Riou *et al.*<sup>7</sup> identified alterations in the calcium sequestering system, specifically the sarcoplasmic reticulum, in a study of the effects of ketamine on contractility and relaxation in a rat papillary muscle preparation. Ketamine impaired isotonic relaxation, contraction-relaxation coupling, and load sensitivity of relaxation, suggesting that ventricular relaxation is directly altered at a cellular level by this intravenous anesthetic. Most recently, Cook *et al.*<sup>9</sup> observed decreases in isotonic relaxation induced by ketamine in an elegant study of the effects of this intravenous anesthetic on contractility in ferret papillary muscle. Although ketamine augmented maximum velocity of lengthening and maximal rate of decrease force in an isometric twitch when adrenergic transmission was intact, pretreatment with reserpine (depleting norepinephrine stores) resulted in significant decreases in these variables, implying that relaxation is directly delayed when normal adrenergic synaptic function is impaired. Similar findings were reported by Urthaler *et al.*<sup>10</sup> in canine ventricular trabeculae in the presence of pretreatment with  $\alpha$  and  $\beta$  adrenergic antagonists. Thus, experimental evidence *in vitro*<sup>7-10</sup> suggests that ketamine probably alters myocardial function during diastole.

The effects of the new intravenous anesthetic, propofol, on systemic hemodynamics<sup>11-13</sup> and myocardial contractility<sup>14-17</sup> have been described; however, the actions of this drug on diastolic function *in vivo* or *in vitro* remain unexplored. Like barbiturate sedative-hypnotics,

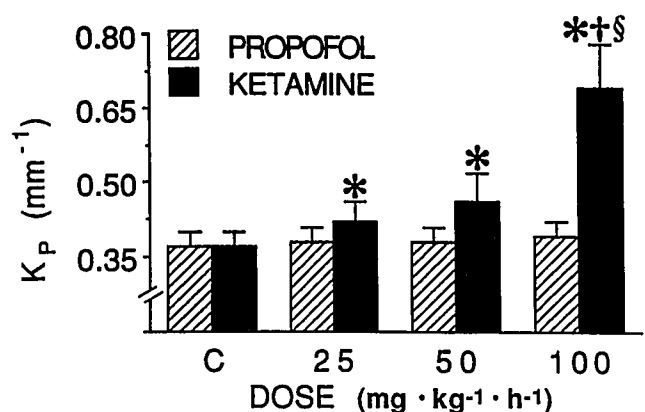


FIG. 2. Effects of ketamine and propofol on regional chamber stiffness ( $K_p$ ). \*Significantly ( $P < 0.05$ ) different from the autonomically blocked, conscious control (C). †Significantly ( $P < 0.05$ ) different from the 25-mg · kg<sup>-1</sup> · h<sup>-1</sup> dose. §Significantly ( $P < 0.05$ ) different from the 50-mg · kg<sup>-1</sup> · h<sup>-1</sup> dose.

propofol has been shown to produce cardiovascular depression and peripheral vasodilation manifested by decreases in cardiac output, systolic and diastolic arterial pressure, and systemic vascular resistance in a variety of experimental and clinical settings.<sup>11</sup> In addition, propofol has been demonstrated to cause concentration-dependent decreases in myocardial contractility as assessed by the end-systolic pressure-length relationship,<sup>15</sup> a relatively load-insensitive measure of contractile state in isolated heart preparations.<sup>31</sup>

The present investigation represents the first study of the effects of intravenous anesthetics on left ventricular diastolic function *in vivo*. The results of this investigation indicate that ketamine profoundly depresses both active (ventricular relaxation) and passive (regional chamber stiffness) phases of diastole in the chronically instrumented dog with autonomic nervous system blockade. Dose-dependent increases in the time constant of isovolumetric relaxation occurred when ketamine was administered, indicating direct prolongation of this phase of diastole. Ketamine also significantly increased regional chamber stiffness in a dose-dependent fashion, indicating that this intravenous anesthetic may also significantly alter the passive filling properties of the left ventricle. The results of this investigation support previous findings *in vitro*<sup>7-10</sup> that imply that ketamine produces direct negative lusitropic effects independent of normal adrenergic transmission by altering intracellular calcium handling. No alteration of diastolic function as measured by isovolumetric relaxation or passive diastolic compliance were observed with propofol with any dose, despite the fact that propofol produced a hemodynamic profile that was very similar to that of ketamine with the doses of these intravenous anesthetics used in this investigation.

Quantitative description of ventricular function during diastole has received considerable attention in recent years because diastolic mechanics significantly influence overall cardiac performance.<sup>1-3</sup> Measurements of indices of diastolic function, however, are complex and depend on both intrinsic (ventricular relaxation and viscoelastic properties) and extrinsic (right ventricular and septal interactions, pericardial restraint, myocardial blood flow, and diastolic suction) factors as well as variables that normally affect systolic function (heart rate, preload, afterload, and myocardial contractility).<sup>32</sup> Time constants of isovolumetric relaxation have been shown to be variably affected by changes in heart rate and ventricular loading conditions.<sup>2</sup> The direct negative chronotropic actions of ketamine independent of adrenergic transmission have been previously described.<sup>30,33</sup> Thus, the decreases in heart rate observed in the present investigation with ketamine at the 50- and 100-mg  $\cdot$  kg<sup>-1</sup>  $\cdot$  h<sup>-1</sup> doses may partially explain observed increases in the period of isovolumetric relaxation. However, no significant change in heart rate

was observed at the lowest dose of ketamine, indicating that the changes in isovolumetric relaxation observed could not be solely attributed to alterations in heart rate. Interpretation of increases in the time constant of isovolumetric relaxation must be further qualified because ketamine produced other hemodynamic changes, including increases in left ventricular end-diastolic pressure (at the 100-mg  $\cdot$  kg<sup>-1</sup>  $\cdot$  h<sup>-1</sup> dose) and systemic vascular resistance (at the 50- and 100-mg  $\cdot$  kg<sup>-1</sup>  $\cdot$  h<sup>-1</sup> doses). Also, the alterations in heart rate, loading conditions, and myocardial contractility produced by ketamine may have influenced passive viscoelastic properties and diastolic compliance and could not be completely excluded from the analysis.

Decreases in heart rate and myocardial contractility observed with propofol represent uncontrolled variables that may alter the interpretation of the effects of this agent on diastolic function. Although propofol has been reported to produce modest degrees of peripheral vasodilation in experimental animals and humans with intact autonomic nervous system function,<sup>11</sup> no changes in preload (left ventricular end-diastolic pressure) or afterload (calculated systemic vascular resistance) were observed with the administration of propofol in the presence of autonomic blockade with current investigation. These findings suggest that propofol does not directly alter isovolumetric relaxation and diastolic compliance, but this conclusion may require some qualification when this drug is administered in the presence of intact autonomic reflexes.

The doses of ketamine and propofol used in this investigation were chosen to provide reliable anesthesia in all animals and to establish similar cardiovascular dose-response relationships. The lower doses of each drug correlate well with those previously described for canine anesthesia.<sup>13,34</sup> Although identical doses of ketamine and propofol produced similar hemodynamic actions, no direct conclusion about the relative anesthetic potencies of these intravenous anesthetics should be inferred. In addition, plasma concentrations of ketamine and propofol were not obtained in this investigation, therefore, direct comparison of the effects of these agents between the chronically instrumented canine model and humans may be difficult and should be approached cautiously.

In summary, the results of this investigation indicate that ketamine prolongs isovolumetric relaxation and produces a decrease in ventricular compliance as evaluated by regional chamber stiffness in chronically instrumented dogs with pharmacologic blockade of the autonomic nervous system. In contrast, propofol has no effect on left ventricular diastolic function although it produces very similar systemic hemodynamic effects at the doses used in this experimental preparation. The present results for ketamine are supported by investigations *in vitro*<sup>7-10</sup> that

suggest that ketamine may directly alter intracellular calcium kinetics during both systole and diastole, inducing decreases in contractile state and prolongation of relaxation, respectively. Extension of the findings of this investigation to the clinical setting suggests that acute cardiac decompensation observed in catecholamine-depleted, critically ill patients when ketamine is used as an anesthetic induction agent<sup>28</sup> may be partially attributed to direct alterations in left ventricular diastolic function. Such a comparison must be viewed with caution, however, since the doses of ketamine and propofol used in this investigation may exceed those typically used in clinical practice.

The authors extend their appreciation to John Tessmer, Doug Hettrick, and David Schwabe for technical assistance and to Mimi Mick and Suzanne Emmrich for preparation of the manuscript.

### References

1. Harizi RC, Bianco JA, Alpert JS: Diastolic function of the heart in clinical cardiology. *Arch Intern Med* 148:99-109, 1988
2. Lew WY: Evaluation of left ventricular diastolic function (editorial). *Circulation* 79:1393-1397, 1989
3. Grossman W: Diastolic dysfunction and congestive heart failure. *Circulation* 81(suppl 2):III 1-7, 1990
4. Dougherty AH, Naccarelli GV, Gray EL, Hicks CH, Goldstein RA: Congestive heart failure with normal systolic function. *Am J Cardiol* 54:778-782, 1984
5. Humphrey LS, Stinson DC, Humphrey MJ, Finney RS, Zeller PA, Judd MR, Blanck TJ: Volatile anesthetic effects on left ventricular relaxation in swine. *ANESTHESIOLOGY* 73:731-738, 1990
6. Pagel PS, Kampine JP, Schmeling WT, Warltier DC: Alteration of left ventricular diastolic function by desflurane, isoflurane, and halothane in the chronically instrumented dog with autonomic nervous system blockade. *ANESTHESIOLOGY* 74:1103-1114, 1991
7. Riou B, Lecarpentier Y, Viars P: Inotropic effect of ketamine on rat cardiac papillary muscle. *ANESTHESIOLOGY* 71:116-125, 1989
8. Rusy BF, Amuzu JK, Bosscher HA, Redon D, Komai H: Negative inotropic effect of ketamine in rabbit ventricular muscle. *Anesth Analg* 71:275-278, 1990
9. Cook DJ, Carton EG, Housmans PR: Mechanism of the positive inotropic effect of ketamine in isolated ferret ventricular papillary muscle. *ANESTHESIOLOGY* 74:880-888, 1991
10. Urthaler F, Walker AA, James TN: Comparison of the inotropic action of morphine and ketamine studied in canine cardiac muscle. *J Thorac Cardiovasc Surg* 72:142-149, 1976
11. Sebel PS, Lowdon JD: Propofol: A new intravenous anesthetic. *ANESTHESIOLOGY* 71:260-277, 1989
12. Coates DP, Monk CR, Prys-Roberts C, Turtle M: Hemodynamic effects of infusions of the emulsion formulation of propofol during nitrous oxide anesthesia in humans. *Anesth Analg* 66:64-70, 1987
13. Goodchild CS, Serrao JM: Cardiovascular effects of propofol in the anesthetized dog. *Br J Anaesth* 63:87-92, 1989
14. Brussel T, Theissen JL, Vigfusson G, Lunkenheimer PP, Van Aken H, Lawin P: Hemodynamic and cardiodynamic effects of propofol and etomidate: Negative inotropic properties of propofol. *Anesth Analg* 69:35-40, 1989
15. Coetzee A, Fourie P, Coetzee J, Badenhorst E, Bolliger C, Uebel R, Wium C, Lombard C: Effects of various propofol plasma concentrations on regional myocardial contractility and left ventricular afterload. *Anesth Analg* 69:473-483, 1989
16. Lepage JY, Pinaud ML, Helias JH, Juge CM, Cozian AY, Farinotti R, Souron RJ: Left ventricular function during propofol and fentanyl anesthesia in patients with coronary artery disease: Assessment with a radionuclide approach. *Anesth Analg* 67:949-955, 1988
17. Mulier JP, Wouters PF, Van Aken H, Vermaut G, Vandermeersch E: Cardiodynamic effects of propofol in comparison with thiopental: Assessment with a transesophageal echocardiographic approach. *Anesth Analg* 72:28-35, 1991
18. White PF, Way WL, Trevor AJ: Ketamine: Its pharmacology and therapeutic uses. *ANESTHESIOLOGY* 56:119-136, 1982
19. Ivankovich AD, Miletich DJ, Reimann C, Albrecht RF, Zahed B: Cardiovascular effects of centrally administered ketamine in goats. *Anesth Analg* 53:924-931, 1974
20. Lundy PM, Gverzdys S, Frew R: Ketamine: evidence of tissue specific inhibition of neuronal and extraneuronal catecholamine uptake processes. *Can J Physiol Pharmacol* 63:298-303, 1985
21. Salt PJ, Barnes PK, Beswick FJ: Inhibition of neuronal and extraneuronal uptake of noradrenaline by ketamine in the isolated perfused rat heart. *Br J Anaesth* 51:835-838, 1979
22. Cullen PM, Turtle M, Prys-Roberts C, Way WL, Dye J: Effect of propofol anesthesia on baroreflex activity in humans. *Anesth Analg* 66:1115-1120, 1987
23. Theroux P, Franklin D, Ross J Jr, Kemper WS: Regional myocardial function during acute coronary artery occlusion and its modification by pharmacologic agents in the dog. *Circ Res* 35:896-908, 1974
24. Thompson DS, Waldron CB, Juul SM, Naqvi N, Swanton RH, Coltart DJ, Jenkins BS, Webb-Peploe MM: Analysis of left ventricular pressure during isovolumic relaxation in coronary artery disease. *Circulation* 65:690-697, 1982
25. Raff GL, Glantz SA: Volume loading slows left ventricular isovolumic relaxation rate. Evidence of load-dependent relaxation in the intact dog heart. *Circ Res* 48:813-824, 1981
26. Kurnik PB, Courtois MR, Ludbrook PA: Diastolic stiffening induced by acute myocardial infarction is reduced by early reperfusion. *J Am Coll Cardiol* 12:1029-1036, 1988
27. Schwartz DA, Horwitz LD: Effects of ketamine on left ventricular performance. *J Pharmacol Exp Ther* 194:410-414, 1975
28. Waxman K, Shoemaker WC, Lippmann M: Cardiovascular effects of anesthetic induction with ketamine. *Anesth Analg* 59:355-358, 1980
29. Saegusa K, Furukawa Y, Ogiwara Y, Chiba S: Pharmacologic analysis of ketamine-induced cardiac actions in isolated, blood-perfused canine atria. *J Cardiovasc Pharmacol* 8:414-419, 1986
30. Hall PJ, Pleuvry BJ: An in vitro study of the effects of calcium on the cardiovascular actions of thiopentone, althesin and ketamine in the rat. *J Pharm Pharmacol* 31:460-465, 1979
31. Sagawa K, Suga H, Shoukas AA, Bakalar KM: End-systolic pressure/volume ratio: A new index of ventricular contractility. *Am J Cardiol* 40:748-753, 1977
32. Plotnick GD: Changes in diastolic function: Difficult to measure, harder to interpret. *Am Heart J* 118:637-641, 1989
33. Adams HR, Parker JL, Mathew BP: The influence of ketamine on inotropic and chronotropic responsiveness of heart muscle. *J Pharmacol Exp Ther* 201:171-183, 1977
34. Lumb WV, Jones EW: *Veterinary Anesthesia*. 2nd Edition. Philadelphia, Lea and Febiger, 1984, pp 307-312