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Ketamine Depresses Myocardial Contractility as Evaluated by the Preload Recruitable Stroke Work Relationship in Chronically Instrumented Dogs with Autonomic Nervous System Blockade

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Previous investigations examining the direct actions of ketamine on myocardial contractility *in vivo* suggest that ketamine may produce depression of contractile function under certain circumstances. Such studies have had significant limitations in that reliable, easily quantified, load-independent indices of contractility were not used, and ketamine produces dramatic sympathomimetic pressor effects mediated *via* an intact autonomic nervous system. In the present investigation, eight experiments were performed using dogs chronically instrumented for measurement of aortic and left ventricular pressure, rate of increase of left ventricular pressure (dP/dt), subendocardial segment length, and cardiac output. Contractility was evaluated using the linear relationship between preload recruitable stroke work and end-diastolic segment length. The slope (M_w) and length intercept of this relationship, and two derived variables, preload recruitable work area (PRWA) and stroke work at constant end-diastolic length (SWEDL), were used as indices of contractility. Pharmacologic blockade of the autonomic nervous system was instituted in all experiments since a portion of the systemic hemodynamic actions of ketamine are secondary to stimulation of the autonomic nervous system. Systemic hemodynamics and indices of contractile function were recorded and evaluated in the conscious state and after a 20-min equilibration at 25-, 50-, and 100-$mg \cdot kg^{-1} \cdot h^{-1}$ infusions of ketamine. A significant ($P < 0.05$) and dose-dependent decrease in M_w (68 ± 7 during control to 41 ± 2 mmHg at 100 $mg \cdot kg^{-1} \cdot h^{-1}$) was observed, demonstrating depression of myocardial contractility. Similar decreases in PRWA (1720 ± 690 during control to 280 ± 50 $mmHg \cdot mm^2$ at 100 $mg \cdot kg^{-1} \cdot h^{-1}$) and SWEDL (421 ± 80 during control to 135 ± 8 $mmHg \cdot mm$ at 100 $mg \cdot kg^{-1} \cdot h^{-1}$) were also observed. Concomitant decreases in global isovolumetric indices of contractility (left ventricular peak positive dP/dt and dP/dt at 50 mmHg [dP/dt_{50}]), regional myocardial function (percent segment shortening), and cardiac output were also observed. The results indicate that ketamine produces direct decreases in myocardial contractility in chronically instrumented dogs independent of autonomic nervous system activity. (Key words: Anesthetics, intravenous: ketamine. Heart: myocardial contractility; myocardial performance; left ventricular function; preload recruitable stroke work; ventricular function.)

SINCE ITS INTRODUCTION into clinical practice 21 yr ago, ketamine has been used with widespread success in the anesthetic induction of certain patients with hemodynamic compromise.[1] The observation that ketamine can lead to cardiodepressant actions in a subset of critically ill patients[2] has stimulated exploration of the direct effects of this intravenous anesthetic on cardiovascular function. The increases in heart rate and arterial pressure associated with administration of ketamine have been attributed to the central and peripheral sympathomimetic actions of this drug *via* blockade of reuptake of norepinephrine in adrenergic nerves.[3,4] Cardiac decompensation after administration of ketamine in some patients has been suggested to be due to depletion of catecholamines leading to exposure of the direct vasodilatory and myocardial depressant actions of ketamine independent of sympathomimetic effects.[2,5] Nevertheless, the direct effects of ketamine on myocardial contractility *in vivo*[2,5–9] have been difficult to interpret because of two persistent difficulties: first, the indices of inotropic state used in previous studies are either indirect indicators of contractile function or are significantly dependent ventricular loading conditions, and second, changes in contractility are often masked by ketamine-induced pressor effects. The majority of studies *in vitro* support the contention that ketamine possesses negative inotropic properties,[10–19] but this conclusion remains controversial because some investigations have implied that ketamine may in fact exert direct positive inotropic effects.[18–23]

The purpose of this investigation was to reexamine the effects of ketamine on myocardial contractility in chronically instrumented dogs using techniques designed to overcome deficiencies with previously used indices of contractility and to eliminate interactions between ketamine and the autonomic nervous system. Contractility was evaluated using the preload recruitable stroke work (PRSW) *versus* end-diastolic segment length (EDL) rela-

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tionship. This technique has been shown to be a sensitive, easily quantified, and relatively afterload-independent index of myocardial contractile function in conscious[24,25] and anesthetized[25] dogs. In addition, the experiments in this investigation were performed in the presence of pharmacologic blockade of the autonomic nervous system because ketamine produces dramatic pressor effects mediated *via* an intact autonomic nervous system.[1,3,4,9] Therefore, the direct actions of ketamine on myocardial contractility were evaluated independent of any indirect sympathomimetic effects.

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 is described in detail elsewhere.[25] Briefly, eight conditioned mongrel dogs weighing between 25 and 31 kg were fasted overnight and anesthetized with sodium thiamylal (10 mg/kg). Following tracheal intubation, anesthesia was maintained with enflurane (2.0–3.0%) in 100% oxygen (1 l/min) *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. The peak rate of increase of left ventricular pressure (dP/dt) and the rate of increase of ventricular pressure at 50 mmHg (dP/dt_{50}), indices of global myocardial contractility, were obtained by electronic differentiation of the left ventricular pressure waveform. 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_{50} pressure transducer, Oxnard, CA). A hydraulic vascular occluder (In Vivo Metric, Healdsburg, CA) was placed around the inferior vena cava for abrupt alteration of left ventricular preload. 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. 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 $mg \cdot kg^{-1}$ intramuscularly). Antibiotic prophylaxis consisted of intramuscular procaine penicillin G (25,000 $U \cdot kg^{-1}$) and gentamicin (4.5 $mg \cdot kg^{-1}$). Dogs were allowed to recover for a minimum of 7 days prior to experimentation. During the postoperative period, the dogs were trained to stand quietly in a sling during hemodynamic monitoring. Segment length signals were driven and monitored by ultrasonic amplifiers (Hartley, Houston, TX). End-systolic segment length (ESL) was determined at maximum negative left ventricular dP/dt and EDL was determined at the onset of left ventricular isovolumetric contraction. The lengths were normalized according to the method described by Theroux *et al.*[26] Percent segment shortening (%SS) was calculated by use of the equation: $\%SS = (EDL - ESL) \times 100/EDL$. 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

All dogs (n = 8) were fasted overnight, and fluid deficits were replaced before experimentation with crystalloid (500 ml 0.9% normal saline). Maintenance fluids (0.9% normal saline) were continued at 3 $mg \cdot kg^{-1} \cdot h^{-1}$ for the duration of each experiment. After instrumentation was calibrated and baseline hemodynamic data were recorded, the autonomic nervous system was pharmacologically blocked with intravenous propranolol (2 $mg \cdot kg^{-1}$), atropine methylnitrate (3 $mg \cdot kg^{-1}$), and hexamethonium (20 $mg \cdot kg^{-1}$). Adequacy of autonomic blockade was demonstrated by lack of reflex changes in heart rate after an abrupt decrease in venous return *via* inflation of the inferior vena caval hydraulic vascular occluder prior to and following completion of the experiment.

Alteration of left ventricular preload was used to generate left ventricular pressure–segment length loops in the conscious state and after administration of ketamine.

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After control hemodynamics had been recorded and autonomic nervous system blockade had been completed, the inferior vena cava was abruptly occluded to reduce left ventricular systolic pressure approximately 25–30 mmHg over 20–25 cardiac cycles (fig. 1). The resultant ventricular pressure–segment length loops were recorded on the digital oscilloscope. No changes in heart rate were observed in response to occlusion of the inferior vena cava in any experiment, and the occlusion of the inferior vena cava was released immediately after the pressure–segment length loops were recorded. End-expiratory ventricular pressure–segment length loops were identified and used for analysis of myocardial contractility.

After hemodynamics and ventricular pressure–segment length loops had been recorded in the conscious, autonomically blocked state, anesthesia was induced with intravenous bolus of ketamine (10 mg · kg^{-1}). The trachea was intubated, and anesthesia was maintained with a continuous infusion of ketamine at 25, 50, or 100 mg · kg^{-1} · h^{-1} in a random fashion. Each dog's lungs were mechanically ventilated with a nitrogen (79%) and oxygen (21%) mixture at a total gas flow rate of 2 l · min^{-1}. After 20 min of equilibration at a given dose of ketamine, hemodynamics were recorded, and ventricular pressure–segment length loops were obtained in the manner described above. The continuous infusion dose of ketamine 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 throughout each experiment.

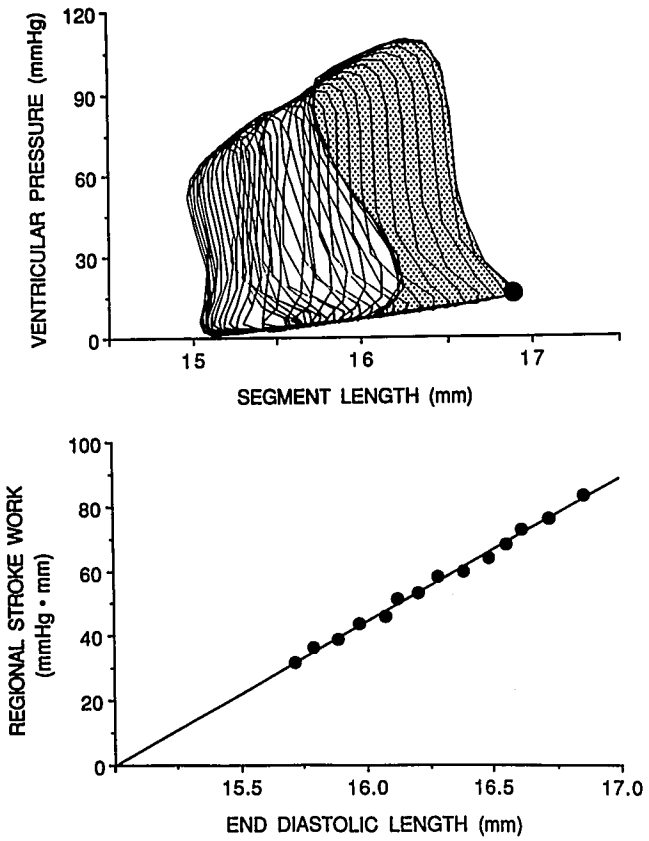

FIG. 1. The method used to calculate the preload recruitable stroke work (PRSW) *versus* end-diastolic length (EDL) relationship. Pressure length loops were generated by abrupt occlusion of the inferior vena cava resulting in segmental decreases in ventricular pressure over 20–25 cardiac cycles. The area of each loop (shaded area), calculated by electronic integration and corresponding to regional stroke work, was plotted against the corresponding end-diastolic length (large dot) for each loop (*top*). A linear regression analysis was then used to define the PRSW *versus* EDL relationship (*bottom*).

Myocardial contractility was evaluated using the PRSW *versus* EDL relationship.[24,25] A series of 20–25 ventricular pressure–segment length loops were obtained during steady-state hemodynamic conditions in the autonomically blocked, conscious state and at each dose of ketamine. The area of each loop, corresponding to segmental stroke work (PRSW), was calculated by electronic integration. The EDL of each loop was identified on the oscilloscope, digitally amplified to increase precision and converted to the appropriate units (millimeters) by use of a linear formula generated with voltage–segment length calibration data. The PRSW was then plotted against the corresponding EDL for each loop (fig. 1). Linear regression analysis was used to describe the PRSW *versus* EDL slope (M_w) and length intercept (L_w).

The relationship between regional stroke work (PRSW) and EDL (preload) is analogous to traditional Frank-Starling ventricular performance curves relating cardiac output or stroke work to various measures of preload (most commonly, left ventricular end-diastolic pressure or pulmonary artery capillary wedge pressure). Though descriptively useful, Frank-Starling curves are nonlinear, difficult to quantitatively evaluate, and significantly dependent on changes in afterload,[27] rendering these measures of ventricular function strictly imprecise for attempts to quantify alterations in myocardial contractility. The PRSW *versus* EDL relationship, in contrast, has been shown previously to be a linear (and therefore, easily quantified) and relatively afterload-insensitive index of inotropic state in conscious,[24,25] anesthetized,[25] and post-ischemic–reperfused[28] canine myocardium. Increases in myocardial contractility are reflected by increases in M_w or decreases in L_w, alterations that are analogous to shifting of the Frank-Starling curve "up." Similarly, decreases in contractile state are manifested by decreases in M_w or increases in L_w (a phenomenon known as "diastolic creep"[28]). Shifts in the PRSW *versus* EDL line below or to the right of control imply that less segmental stroke work is accomplished at any given preload, reflecting a decrease in intrinsic contractility analogous to shifting of the Frank-Starling curve "down."

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Because changes in inotropic state can be reflected in either M_w or L_w variables,[28] myocardial contractility was also quantitated using two techniques that combined these parameters. Following the method of Glower *et al.*,[28] preload recruitable work area (PRWA) was defined as the area under the PRSW *versus* EDL regression line:

$$PRWA = \frac{M_w}{2}(1.2\ L_{w\ max} - L_w)^2$$

where $L_{w\ max}$ = the maximum x-intercept obtained for each experiment. As suggested by Glower *et al.*,[28] the factor of 1.2 was chosen such that PRWA remained positive in all experiments with all interventions (fig. 2). In addition, stroke work at a constant EDL of 1.2 $L_{w\ max}$ (SWEDL) was calculated using the formula:

$$SWEDL = M_w(1.2\ L_{w\ max} - L_w)$$

Statistical Analysis

Statistical analysis of data during the conscious state with and without autonomic nervous system blockade and following administration of ketamine was performed by analysis of variance with repeated measures followed by application of Bonferroni's modification of the *t* test. Changes were considered statistically significant when the probability (*P*) value was less than 0.05. All data were expressed as mean ± standard error of the mean.

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, stroke volume, and systemic vascular resistance (table 1). No changes were observed in the rate–pressure product, left ventricular end-diastolic pressure, or cardiac output. Regression coefficients obtained for the calculation of the PRSW *versus* EDL relationship were ≥ 0.975 in the conscious and anesthetized states.

Ketamine produced significant ($P < 0.05$) increases in left ventricular end-diastolic pressure and systemic vascular resistance in the presence of autonomic nervous system blockade. Heart rate, left ventricular systolic pressure, and rate–pressure product decreased slightly, but these changes were significant only at the 100-mg·kg^{-1}·h^{-1} dose of ketamine (table 1). No changes in mean arterial pressure were observed with the administration of ketamine in this preparation. Ketamine caused significant and dose-related decreases in cardiac output (3.0 ± 0.2 during control to 1.8 ± 0.2 l·min^{-1} at the 100-mg·kg^{-1}·h^{-1} dose).

The effects of ketamine on multiple indices of myocardial contractility are summarized in table 2 and figure 3. M_w decreased in a dose-dependent fashion following administration of ketamine (68 ± 7 during control to 41 ± 2 mmHg at the 100-mg·kg^{-1}·h^{-1} dose), quantitatively

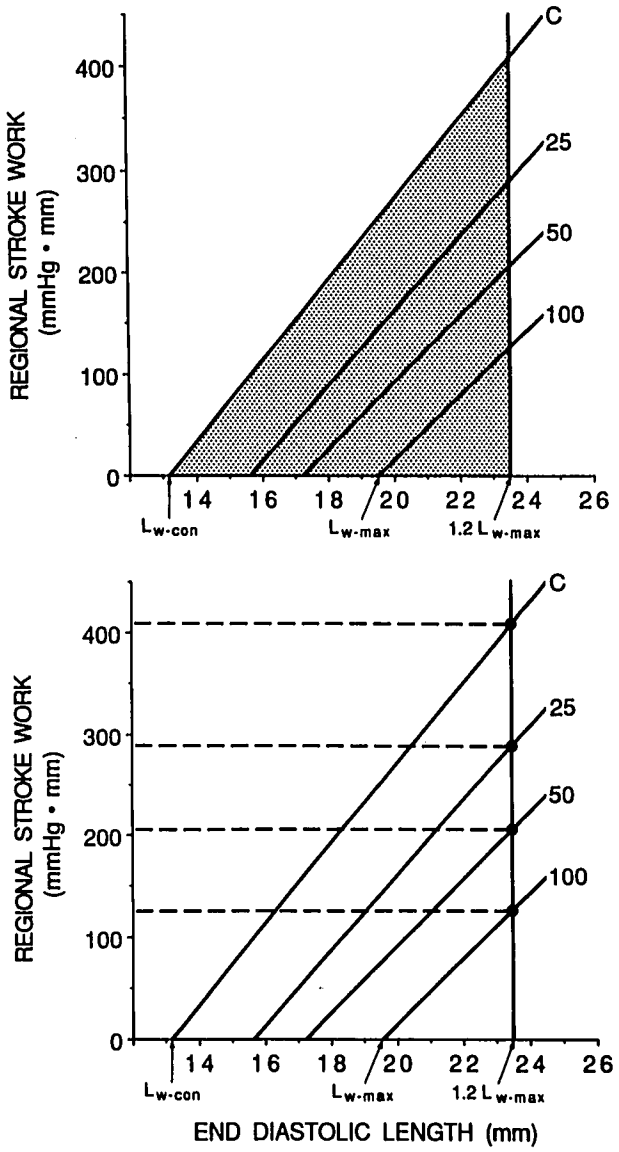

FIG. 2. Methods used to calculate preload recruitable work area (PRWA, *top*) and stroke work at constant end-diastolic length (SWEDL, *bottom*). The area beneath the preload recruitable stoke work (PRSW) *versus* end-diastolic length (EDL) line for the conscious control (C) was calculated using the corresponding length intercept ($L_{w\text{-}con}$) and 1.2 times the maximum length intercept ($L_{w\text{-}max}$) obtained with subsequent interventions as the limits of integration (see text). Interventions reducing contractility (*e.g.*, ketamine [25, 50, 100 mg·kg^{-1}·h^{-1}]) would be expected to shift the PRSW *versus* EDL line to the right of or below the control. PRWA corresponding to each anesthetic intervention was obtained using the corresponding length intercept and 1.2 times $L_{w\text{-}max}$ as described for the conscious control. SWEDL (*bottom*) was obtained by calculating stroke work at 1.2 $L_{w\text{-}max}$ for the conscious control and each anesthetic intervention (large dots and corresponding dashed lines).

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TABLE 1. Effects of Ketamine on Systemic Hemodynamics

	Conscious Pre-ANS Block	Conscious Post-ANS Block	Ketamine Dose (mg·kg^{-1}·h^{-1})		
			25	50	100
HR (beats·min^{-1})	86 ± 4*	110 ± 5	100 ± 6	98 ± 6	93 ± 6*
MAP (mmHg)	106 ± 4*	72 ± 6	75 ± 6	74 ± 7	64 ± 6
RPP (beats·min^{-1}·mmHg·10^3)	11.4 ± 0.5	10.1 ± 0.9	9.2 ± 0.9	8.8 ± 1.0	7.2 ± 0.8*
LVSP (mmHg)	136 ± 3*	97 ± 5	97 ± 6	95 ± 7	85 ± 5*
LVEDP (mmHg)	10 ± 1	7 ± 1	10 ± 1	11 ± 1	13 ± 1*
CO (l/min)	2.9 ± 0.2	3.0 ± 0.2	2.4 ± 0.1*	2.1 ± 0.2*	1.8 ± 0.2*†
SVR (dyn·s·cm^{-5})	3060 ± 280*	1990 ± 170	2580 ± 270	2840 ± 260*	2930 ± 280*
SV (ml)	34 ± 2*	27 ± 1	23 ± 1	21 ± 1*	19 ± 1*

All data are mean ± SEM; n = 8.

HR = heart rate; MAP = mean arterial pressure; RPP = rate pressure product; LVSP = left ventricular systolic pressure; LVEDP = left ventricular end diastolic pressure; CO = cardiac output; SVR = systemic vascular resistance; SV = stroke volume; ANS = autonomic nervous sytem.

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

† Significantly ($P < 0.05$) different from the 25-mg·kg^{-1}·h^{-1} dose.

indicating a direct negative inotropic effect. A significant increase in L_w was noted only at the highest dose of ketamine. Depression of myocardial contractile function was also identified, using two techniques that incorporate both M_w and L_w variables. PRWA and SWEDL also decreased in a dose-dependent fashion during infusion of ketamine (1720 ± 690 during control to 280 ± 50 mmHg·mm^2 and 421 ± 80 during control to 135 ± 8 mmHg·mm at the 100-mg·kg^{-1}·h^{-1} dose, respectively). Concomitant decreases in peak positive left ventricular dP/dt (1780 ± 170 during control to 860 ± 90 mmHg/s at 100 mg·kg^{-1}·h^{-1}) and dP/dt_{50} (1630 ± 120 during control to 800 ± 80 mmHg/s at 100 mg·kg^{-1}·h^{-1}) were observed. Regional contractility as evaluated by percent segment shortening also declined (figure 3).

Discussion

The effects of ketamine on cardiac function have been examined in both intact[2,5–9] and isolated heart preparations,[10–23] and yet the direct action of this intravenous anesthetic on myocardial contractility remains controversial. Initial studies in humans and experimental animals described the cardiostimulatory properties of ketamine. Traber *et al.*[6] demonstrated that ketamine produced dose-dependent increases in heart rate, mean arterial pressure, and cardiac output in acutely instrumented dogs. Tweed *et al.*[7] and Idvall *et al.*[8] reported similar results in human volunteers and noted that ketamine appeared to enhance myocardial contractility as indicated by an increase in cardiac index associated with a concomitant decrease in left ventricular end-diastolic pressure. Ivankovich *et al*[9] confirmed these findings and showed that ketamine produced sympathomimetic actions *via* direct stimulation of the central nervous system. In contrast, Schwartz and Horwitz[5] used propranolol and atropine to blunt autonomic nervous system tone in chronically instrumented dogs and demonstrated that ketamine produced a brief but significant myocardial depressant effect as evaluated by decreases in left ventricular peak positive dP/dt, car-

TABLE 2. Effects of Ketamine on Contractile Function

	Conscious Pre-ANS Block	Conscious Post-ANS Block	Ketamine Dose (mg·kg^{-1}·h^{-1})		
			25	50	100
dP/dt (mmHg/s)	2680 ± 180*	1780 ± 170	1410 ± 100	1230 ± 100*	860 ± 90*†
dP/dt_{50} (mmHg/s)	2060 ± 110*	1630 ± 120	1290 ± 80*	1140 ± 90*	800 ± 80*†‡
SS (%)	13.4 ± 1.1	13.3 ± 0.8	11.3 ± 0.6	9.7 ± 0.5*	7.1 ± 0.7*†‡
M_w (mmHg)	—	68 ± 7	53 ± 6*	46 ± 6*†	41 ± 2*†
L_w (mm)	—	14.8 ± 0.8	15.2 ± 0.9	15.7 ± 0.9	18.0 ± 1.3*†‡
PRWA (mmHg·mm^2)	—	1720 ± 690	1250 ± 480*	1020 ± 420*†	280 ± 50*†‡
SWEDL (mmHg·mm)	—	421 ± 80	339 ± 66*	296 ± 63*†	135 ± 8*†‡

All data are mean ± SEM; n = 8.

SS = segment shortening; M_w and L_w = preload recruitable stroke work *versus* end-diastolic length slope and length intercept, respectively; PRWA = preload recruitable work area; SWEDL = stroke work at constant end-diastolic length; ANS = autonomic nervous system.

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

† Significantly ($P < 0.05$) different from the 25-mg·kg^{-1}·h^{-1} dose.

‡ Significantly ($P < 0.05$) different from the 50-mg·kg^{-1}·h^{-1} dose.

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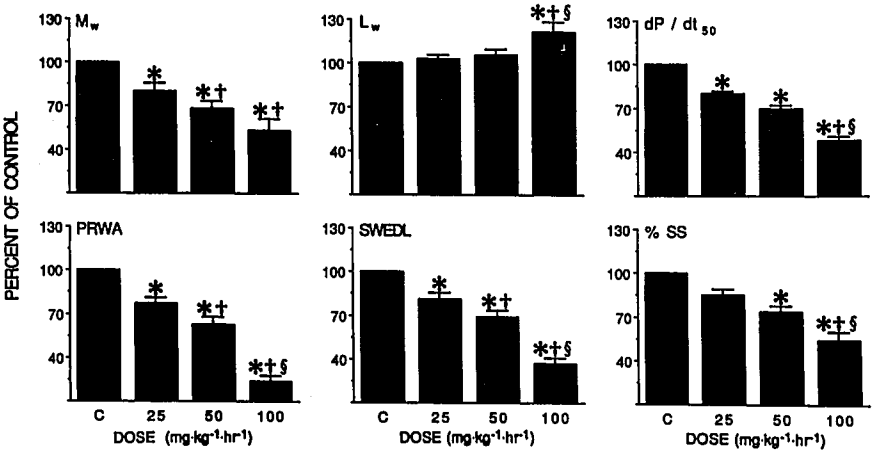

FIG. 3. Effects of ketamine on indices of contractile function. *Significantly ($P < 0.05$) different from conscious, postautonomic nervous system blockade control (C). †Significantly ($P < 0.05$) different from the 25-mg·kg^{-1}·h^{-1} dose of ketamine. §Significantly ($P < 0.05$) different from the 50-mg·kg^{-1}·h^{-1} dose of ketamine. M_w and L_w = preload recruitable stroke work *versus* end-diastolic length slope and length intercept, respectively; PRWA = preload recruitable work area; SWEDL = stroke work at constant end diastolic length; %SS = percent segment shortening.

diac output, and stroke volume and increases in left ventricular end-diastolic pressure. Depression of cardiac function by ketamine was first identified in humans by Waxman *et al.*,[2] who showed that ketamine can lead to acute cardiovascular decompensation when used for induction in critically ill and acutely traumatized patients. Thus, although ketamine produces dramatic increases in heart rate, mean arterial pressure, and cardiac output consistent with sympathomimetic effects under normal circumstances, ketamine also may produce direct myocardial depressant effects *in vivo* in the absence of central and peripheral adrenergic transmission.[2,5]

The majority of studies *in vitro* support the contention that ketamine produces direct negative inotropic effects; however, this conclusion is not without controversy. Early studies by Dowdy and Kaya,[10] Berry,[11] Chang,[12] and Goldberg *et al.*[13] conducted in isolated rabbit, chicken embryo, guinea pig, and rat hearts, respectively, demonstrated decreases in contractility in response to ketamine. These findings were supported by other studies[14–17] in a variety of preparations, the most recent by Rusy *et al.*[17] in rabbit papillary muscle. In contrast, other authors[18–23] have suggested that ketamine may produce positive inotropic effects *in vitro*. Urthaler *et al.*[18] demonstrated increases in maximum unloaded shortening velocity and in maximum rate of tension increase with low concentrations of ketamine in canine trabeculae. However, the authors[18] noted decreases in contractility in this preparation at higher concentrations of ketamine, as well as at all concentrations when dogs had been chronically pretreated with propranolol or reserpine. Experiments in canine[19] and rat atria[20,21] also demonstrated positive ionotropic actions in response to lower concentrations of ketamine that were, in some cases, reversed by pretreatment with propranolol or imipramine. It should be noted, however, that changes in atrial performance may not reflect alterations in excitation–contraction coupling induced in ventricular muscle.

Most recently, Riou *et al.*[22] showed that ketamine produced increases in maximum unloaded shortening velocity, maximum rate of isometric active force, and maximum isometric force in rat papillary muscle. In contrast to the findings of Urthaler *et al.*[18] and Saegusa *et al.*,[19] ketamine-mediated increases in contractility were not blocked by pretreatment with α- (phentolamine) or β- (propranolol) adrenergic antagonists. Using similar indices of contractility, Cook *et al.*[23] also demonstrated increases in ionotropic state in response to ketamine in an isolated ferret papillary muscle model. In contrast to the findings of Riou *et al.*,[22] however, these investigators[23] showed that the positive ionotropic effects of ketamine were blocked by chronic pretreatment with propranolol or desmethylimipramine, a norepinephrine reuptake inhibitor. Cook *et al.*[23] concluded that ketamine could produce either positive or negative ionotropic actions dependent upon the presence of an intact sympathetic neuroeffector junction or impairment of adrenergic transmission, respectively. Thus, although the findings of the majority of previous investigations *in vitro* suggest that ketamine produces direct negative inotropic effects when the competing actions of centrally mediated or direct peripheral sympathetic stimulation are eliminated,[18,19,23] some existing evidence *in vitro* demonstrates a positive ionotropic response to ketamine even when adrenergic transmission is pharmacologically removed as a confounding variable.[22] A summary of previous investigations examining the effects of ketamine on myocardial contractility *in vivo* and *in vitro* is outlined in table 3.

The results of this investigation indicate that ketamine produces dose-dependent decreases in myocardial contractility as evaluated by the PRSW *versus* EDL relationship and derived variables. M_w demonstrated decreases in contractility of approximately 20; 32, and 47% (change from the conscious state) when ketamine was administered in 25-, 50-, and 100-mg·kg^{-1}·h^{-1} doses, respectively. Even more profound depression of contractile function

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TABLE 3. Investigations of Ketamine on Normal Myocardial Contractile Function

Investigators	Preparation	Indices of Contractility	Effects of Ketamine	Comments
In Vivo				
Tweed *et al.*[7]	Humans	CO, SV	↑	Volunteers
Traber *et al.*[6]	Dogs	CO	↑	—
Schwartz and Horwitz[5]	Chronically instrumented dogs	dP/dt, CO, SV	↔	Contractility decreased by propranolol and atropine
Ivankovich *et al.*[9]	Chronically instrumented goats	CO	↑	Positive ionotropic effects blocked by pentobarbital anesthesia
Idvall *et al.*[8]	Humans	CO	↑	Volunteers
Waxman *et al.*[2]	Humans	CI, LVSW	↓	Patients in intensive care unit
In Vitro				
Riou *et al.*[22]	Rat papillary muscle	V_{max}, dF/dt_{max}, AF/s	↑	Increased contractility not blocked by propranolol or phentolamine
Cook *et al.*[23]	Ferret papillary muscle	DL, dF/dt_{max}, V_{max}	↑	Increased contractility blocked by propranolol or desmethylimipramine
Hall and Pleuvry[21]	Rat atrium	Contraction amplitude	↑	—
Barrigon *et al.*[20]	Rat atrium	dF/dt_{max}, peak contractile force	↑	Positive inotropic effects blocked by verapamil
Urthaler *et al.*[18]	Canine trabeculae	V_{max}, MRTR, TLAT, TMRT, TMXV	↑ at low doses ↓ at high doses	Contractility decreased at all concentrations with propranolol or reserpine pretreatment
Saegusa *et al.*[19]	Isolated canine atrium	Contractile force	↑ at low doses ↓ at high doses	Positive ionotropic effects blocked by propranolol or imipramine
Rusy *et al.*[17]	Rabbit papillary muscle	V/S, rested-state contractions	↓	—
Adams *et al.*[16]	Guinea pig atrium	CT	↓	Occurred in both spontaneously beating and paced atria
Davis and McCans[15]	Isolated rabbit heart	dF/dt_{max}	↓	—
Aronson and Hanno[14]	Isolated rat heart	Isometric systolic tension	↓	—
Chang[12]	Isolated guinea pig heart	Force of contraction	↓	—
Goldberg *et al.*[13]	Rat trabeculae	V_{max}, isometric tension	↓	—
Dowdy and Kaya[10]	Isolated rabbit heart	CT	↓	—
Berry[11]	Embryonic chicken heart	Force of contraction	↓	Occurred in both noninnervated (4-day-old) and innervated (7-day-old) hearts

V_{max} = maximum unloaded shortening velocity; AF/s = maximum isometric force; dF/dt_{max} = maximum rate of isometric active force; DL = peak isotonic shortening; V/S = upstroke velocity of slow action potential; CT = contractile tension; MRTR = maximum rate of tension rise; TLAT = latency time; TMRT = time to maximum rate of tension rise; TMXV = time to maximum velocity of shortening; CO = cardiac output; CI = cardiac index; LVSW = left ventricular stroke work; SV = stroke volume; ↑ = positive inotropic action; ↓ = negative inotropic action; ↔ = no change.

was observed when L_w was incorporated into the calculation of PRWA and SWEDL at higher concentrations of ketamine. Direct negative chronotropic effects of ketamine have been previously described,[16,21] and changes in contractility observed with the PRSW *versus* EDL relationship in this investigation may have been influenced by decreases in heart rate observed at the 100-$mg \cdot kg^{-1} \cdot h^{-1}$ dose of ketamine during autonomic nervous system blockade. However, the decreases in heart rate produced by ketamine were not dose-dependent, and no significant changes in heart rate were observed at the lower doses of ketamine, indicating that the changes in myocardial contractility could not be entirely attributed to alterations in heart rate. In addition, interpretation of decreases in myocardial contractility must be further qualified because significant increases in afterload (as evaluated by calculated systemic vascular resistance) were observed at the 50- and 100-$mg \cdot kg^{-1} \cdot h^{-1}$ doses of ketamine. Although the PRSW *versus* EDL relationship has been shown to be relatively afterload-insensitive,[24] the range of load independence of this contractile index has not been firmly established. Concomitant decreases in left ventricular peak positive dP/dt and dP/dt_{50}, indices of global myocardial contractility, were also observed.

In the present experiments, because of the relative stability of heart rate and ventricular loading conditions, these isovolumetric measures of myocardial contractility are fairly reliable quantitative indicators of contractile state.[25,29] Although the lower doses (25 and 50 $mg \cdot kg^{-1} \cdot h^{-1}$) of ketamine correlate well with those previously described when this agent is used alone for canine anesthesia,[30] no plasma concentrations of ketamine were obtained in this investigation. Therefore, comparison of the direct effects of ketamine on systemic hemodynamics and myocardial contractility between chronically instrumented dogs and humans may be difficult and should be approached cautiously.

The results of the present investigation support the findings of Schwartz and Horwitz.[5] Using an isovolumetric index of myocardial contractility (dP/dt) as well as indirect indicators of contractile state (cardiac output and stroke volume), the authors[5] demonstrated that intravenous ke-

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tamine (4 $mg \cdot kg^{-1}$) briefly decreased myocardial contractility in chronically instrumented dogs pretreated with atropine and propranolol. Interpretation of the results of Schwartz and Horwitz[5] must be qualified, however, because of the following: high baseline heart rates were present in the preparation used; only a very brief time course of ketamine-induced myocardial depression was demonstrated; a dose–response relationship was not established; and the autonomic ganglia (the major conduit for transmission of centrally mediated ketamine-induced increases in sympathetic tone) remained functionally intact. In addition, the indices of contractile function used by Schwartz and Horwitz[5] are highly dependent on preload and afterload,[31] variables that changed significantly with the administration of cocaine. The results of the current investigation also support those of Waxman *et al.*[2] in critically ill patients and the findings of a majority of studies *in vitro* that suggest that ketamine produces direct negative inotropic actions in the absence of normal central or peripheral adrenergic neuronal transmission.[18,19,23]

Cook *et al.*[23] suggested that the species differences in the primary source of myoplasmic calcium may contribute to the conflicting interpretations of the direct actions of ketamine on contractile function *in vitro*. On a cellular level, partial inhibition of normal transsarcolemmal calcium flux may represent the mechanism for direct myocardial depressant effects of ketamine in several species, including the rabbit, ferret, dog (as in the current investigation), and human. Studies by Barrigon *et al.*,[20] Hall and Pleuvry,[21] and Riou *et al.*[22] demonstrated positive inotropic effects of ketamine in preparations of rat myocardium, a tissue that is more dependent on the sarcoplasmic reticulum than the sarcolemma as the primary source for intracellular calcium during contraction.[32] Therefore, Cook *et al.*[23] have speculated that inhibition of transsarcolemmal calcium movement in the rat would be expected to have little impact on overall myocardial contractility in this species, perhaps leading to a positive ionotropic response to ketamine. Further study will be required to clarify this issue, however.

In summary, the present investigation has shown that ketamine produces dose-dependent and easily quantified decreases in myocardial contractility when administered as an intravenous infusion to chronically instrumented dogs with autonomic nervous system blockade. The negative inotropic effect of ketamine is a direct action and occurs independent of the autonomic nervous system. In the presence of intact autonomic nervous system function, however, ketamine may produce positive ionotropic actions directly *via* effects on an intact sympathetic neuroeffector junction[23] or indirectly *via* central nervous system-mediated sympathetic stimulation.[9] While extension of the results of the present investigation to the clinical setting should be approached with caution, the findings suggest that ketamine-induced cardiovascular compromise observed in chronically ill, catecholamine-depleted patients may reflect manifestation of the direct negative ionotropic action of ketamine when normal adrenergic transmission is impaired.

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