Anesthesiology
1998; 88:1202–10

Effects of Ketamine on the Contractility of Failing and Nonfailing Human Heart Muscles In Vitro

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Background: **Induction of anesthesia with ketamine may decrease cardiac output in critically ill patients. The direct effects of ketamine on the failing human myocardium are unknown. This study examined the effects of ketamine on contractility of human failing and nonfailing myocardium *in vitro*.**

Methods: **Trabecular muscles were obtained from the left ventricles and right atria of 10 patients with heart failure undergoing transplantation and from the right atria of 14 patients undergoing coronary artery bypass surgery. Muscles were dissected and mounted in a 37°C bath and stimulated at 1 Hz. Isometric contraction variables were recorded before and after addition of ketamine (concentrations between 0.44 and 440.0 μM) to the bath. The effects of ketamine were compared with those of buffer. To test muscle contractility, at the end of each experiment, 1 μM isoproterenol was added.**

Results: **Ketamine caused a significant dose-dependent decrease in developed tension in nonfailing atrial and failing atrial and ventricular muscles ($P < 0.01$ for all). In vehicle-treated muscles, developed tension remained stable, and isoproterenol increased developed tension 136% (nonfailing atrial muscles) and 178% (failing atrial and ventricular muscles; $P < 0.01$). In nonfailing atrial muscle, isoproterenol restored the ketamine-induced decrease in developed tension toward the baseline value. In failing atrial and ventricular muscles exposed to ketamine, isoproterenol did not counteract the ketamine.**

Conclusions: **Ketamine exerts a direct dose-dependent negative inotropic effect in human heart muscles. The failing myocardium exposed to ketamine has reduced ability to increase contractility even in the presence of increased β-adrenergic stimulation. (Key words: Atrial; cardiomyopathy; congestive heart failure; intravenous anesthetics; ventricular.)**

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Received from the Departments of General Anesthesiology and Thoracic and Cardiovascular Surgery and the Center for Anesthesiology Research, The Cleveland Clinic Foundation, Cleveland, Ohio. Submitted for publication May 14, 1997. Accepted for publication January 13, 1998.

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INDUCTION of anesthesia with ketamine has been reported to maintain good cardiovascular performance in high-risk patients.[1] This effect of ketamine *in vivo* is presumably produced through its sympathomimetic activity, exerted *via* an intact autonomic nervous system.[2] Increases in concentrations of epinephrine and norepinephrine in plasma occur as early as 2 min after intravenous administration of ketamine and return to control levels 15 min later.[3] In the absence of autonomic stimulation, such as in dogs with a pharmacologically blocked autonomic nervous system, infusion of ketamine can decrease cardiac output by 40%.[4] Similarly, not all patients have a stable hemodynamic course with intravenous induction of anesthesia by ketamine. Waxman *et al.*[5] proposed that preoperative stress in severely ill patients may alter the sympathetically mediated physiologic response to ketamine, and the direct myocardial depressant effect of ketamine may predominate. Contrary to the indirect positive inotropic effects occurring *in vivo* in most patients undergoing surgery, the direct *(in vitro)* effects of ketamine on the myocardium are more frequently reported as negative[6–8] than positive.[9,10] These differences have been attributed to the diverse mammalian species used in these experiments or to the wide variety of different tissues that have been studied.[10] Bidwai *et al.*[11] reported that cardiac output decreased when ketamine was administered to patients with no cardiac disease who were undergoing surgery with halothane- or enflurane-induced anesthesia; they concluded that general anesthesia blocks the cardiovascular-stimulating properties of ketamine.

Studies that have examined the effects of ketamine on cardiac contractility *in vitro* have been performed on tissues from various mammalian species[6,7] but rarely on human tissue.[12] Moreover, the effects of ketamine on contractility of the failing human myocardium *in vitro* are unknown. In this study, we examined the direct effects of ketamine on the contractility of failing and functionally normal human myocardium *in vitro*. Indices of myocardial contractility were evaluated over

a wide range of clinically relevant concentrations of ketamine and in supratherapeutic doses, and a significant dose-dependent decrease in isometric contraction was found. Because ketamine can decrease myocardial contractility in critically ill patients (which is generally attributed to the inability of ketamine to further increase sympathetic tone), we also tested the hypothesis that ketamine-induced myocardial depression in end-stage heart disease may be restored by administering the β-adrenergic agonist isoproterenol.

Materials and Methods

Tissue Preparation

This study was approved by the Institutional Review Board at the Cleveland Clinic Foundation. All muscles for this study were obtained from patients undergoing either cardiac transplantation or myocardial revascularization. All operations were performed by a single surgeon (RWS). The first group of muscles, 13 trabecular muscles removed from the right atrial appendages of four patients undergoing cardiac transplantation (seven exposed to ketamine and six to vehicle control) and 26 muscles removed from the left ventricles of nine patients undergoing cardiac transplantation (19 exposed to ketamine and 7 to vehicle control) were obtained from patients with end-stage heart failure. A total of ten patients were in this category, as both atrial and ventricular tissues were used from each of three patients (table 1). The time from heart explantation until mounting of the trabeculae in the baths was 29 ± 2 (SD) min (range, 20–50 min). During transport, the heart was maintained in ice-cold, oxygenated cardioplegic solution with the following composition (in mM): NaCl 147.2, $MgCl_2$, 16.0, KCl 20.0, $NaHCO_3$ 10.0, and $CaCl_2$ 2.25. Once in the laboratory, the heart was placed in cold (8–10°C), oxygenated (95% O_2, 5% CO_2) Krebs-Henseleit buffer with the following composition (in mM): NaCl 100.0, KCl 4.0, $CaCl_2$ 2.5, $MgSO_4$ 1.5, $NaHCO_3$ 20.0, NaH_2PO_4 1.5, sodium acetate 20.0, glucose 10.0, ascorbic acid 0.1, and insulin 5 IU/l. Long, thin trabeculae were dissected carefully from the right atrial appendage or the left ventricle.

The second group of human myocardial trabeculae (n = 66, 58 exposed to ketamine and 8 to vehicle control) was obtained from 14 patients with nonfailing hearts undergoing routine coronary artery bypass graft surgery. Trabecular muscles were dissected from the right atrial appendage, which was removed during surgery for the purpose of cannulation before initiation of cardiopulmonary bypass. The appendage was obtained immediately from the operating room, placed in the cardioplegic solution described here, and taken to the laboratory for dissection of trabeculae. The average time between appendage removal and arrival in the laboratory was 10 min.

Measurement of Isometric Contraction

Isometric contractions were recorded from each muscle as previously described.[13] Spring clips were attached to each end, and the muscle was mounted between a Grass FT-03 force transducer (Grass Instruments, Quincy, MA) and a stationary hook in a water-jacketed tissue bath containing Krebs-Henseleit buffer. The bath was maintained at 37°C and oxygenated with 95% O_2 and 5% CO_2; the gas was directed into the tissue bath through a flow meter, which was set at a constant pressure of 104 mmHg. This gas flow was adjusted for each of the baths, such that the oxygenation of the muscles in all baths was constant and therefore muscle function could be compared. The buffer solution was not recirculated during the experiment. The muscle was allowed to stabilize at minimal resting tension (1–2 mN) with no stimulation for 40 min, during which time the solution in the bath was replaced at 10-min intervals (four replacements) to wash out the cardioplegic solution and to reestablish normal ion gradients after preservation in the cold cardioplegic solution. At the end of this period, the muscle was prestretched to a resting tension of 5–10 mN. Stimulation was initiated through two parallel platinum electrodes that came in contact with the muscle. The stimulation frequency was set at 1 Hz, the duration at 5 ms, and the voltage at 20% higher than the threshold for contraction (usually 2–5 V). The response to stimulation was allowed to stabilize for 30 min. To obtain baseline tension values, the muscle length was increased in increments of 0.1 mm until the length associated with maximal developed tension (L_{max}) was reached (baseline developed tension at L_{max}). At L_{max}, the response again was allowed to stabilize for 20–30 min, by which time stress relaxation was minimized. Contractile variables recorded consisted of the resting tension (tension produced by the muscle in an unstimulated state as a function of its length), developed tension (DT; maximal tension produced by the muscle when stimulated), time to peak tension (time from the beginning of the contraction to the peak response), maximal rate of tension rise and fall (+dT/dt, −dT/dt), and time to half relaxation.

Table 1. Patient Demographic Data, Preoperative Medications, Anesthetics, Preoperative Drug Treatment, and Preoperative Ejection Fraction

Patient No.*	Age/Sex (yr)	Preoperative Medications	Main Anesthetics and Muscle Relaxant	EF (%)
A. Nonfailing atrium (coronary artery bypass grafting patients)				
1	73/M	AM, IS	FEN, ISO, MID, PAN	50
2	47/M	DG, EN	FEN, ISO, MID, PAN	30
3	72/F	None of interest	ISO, FEN, PAN	45
4	70/M	MT	FEN, ISO, MID, PAN	60
5	53/M	NF	FEN, ISO, MID, PAN	60
6	76/M	CP, LB, MT	ETO, FEN, MID, VEC	55
7	72/M	NF	FEN, ISO, PAN	50
8	70/F	AT	ETO, FEN, ISO, MID, VEC	50
9	69/M	DL	ETO, FEN, ISO, MID, PAN	45
10	50/M	AT	ETO, FEN, MID, VAL, PAN	55
11	74/M	AT	ETO, FEN, ISO, MID, PAN	55
12	40/F	AT	FEN, ISO, MID, PAN	60
13	58/F	MT	FEN, ISO, MID, STP, PAN	50
14	69/F	DG, DL, HY, IS	FEN, ISO, MID, PAN	35
B. Failing atrium (heart transplant patients)				
1	37/F	AM, DB, DG, EN, NP	ETO, FEN, MID, PAN	17
2	51/F	AM, DG, LS	ETO, FEN, MID, PAN	10–15
3	61/M	AM, DG, EN, MT	ETO, FENT, ISO, PAN	20
4†	52/M	AM, DG, NP	ETO, FEN, MID, PAN	20
C. Failing ventricle (heart transplant patients)				
1	37/F	AM, DB, DG, EN, NP	ETO, FEN, MID, PAN	17
2	51/F	AM, DG, LS	ETO, FEN, MID, PAN	10–15
3	61/M	AM, DG, EN, MT	ETO, FEN, ISO, PAN	20
4	63/F	AM, DB, DG, EN	ETO, FEN, ISO, PAN	20
5†	53/M	DB, DG	ETO, FEN, ISO, MID, PAN	15
6	55/M	AM, DG, EN	MID, FEN, ISO, PAN	20
7	52/F	DB, DG, EN	FEN, ETO, ISO, PAN	15
8	38/M	DB, DG, LS	FEN, ETO, ISO, PAN	10
9	56/M	DB, DG, HY	MID, ETO, FEN, ISO, PAN	20

M = male; F = female; EF = left ventricular ejection fraction; AM = amiodarone; AT = atenolol; CP = captopril; DB = dobutamine; DG = digoxin; DL = diltiazem; EN = enalapril; HY = hydralazine; IS = isordil; LB = labetalol; LS = lisinopril; MT = metoprolol; NF = nifedipine; NP = sodium nitroprusside; FEN = fentanyl; ISO = isoflurane; MID = midazolam; ETO = etomidate; PAN = pancuronium; vec = vecuronium; stp = sodium thiopental.

The anesthetics are listed in alphabetical order.

* Patients 1, 2, and 3 in categories B and C are the same patients.

† Patient with ischemic cardiomyopathy; all other had dilated cardiomyopathy.

Once the response was stable at L_{max}, ketamine (Ketamine HCl; Parke-Davis, Morris Plains, NJ) was added. Doses of ketamine were added cumulatively to the bath in concentrations between 0.44 and 440.0 μM. These concentrations were used to encompass the wide range of clinically used ketamine dosages and subtherapeutic and supratherapeutic dosages and were calculated based on the concentration that would be found ideally in the plasma (in the absence of effects of redistribution and of protein binding *in vivo*) of a 70-kg adult, with a blood volume of 5.5 l. The effects of ketamine were compared with those of vehicle control (buffer solution). After the dose-response curve to ketamine was completed, a single dose of 1 μM isoproterenol, a β-adrenergic agonist, was added to the bath to determine the residual inotropic response of cardiac muscle in the presence and absence (vehicle control) of ketamine. This concentration of isoproterenol was chosen because it produces a maximal inotropic response in human trabecular muscles.[14,15] The muscle was not washed between exposure to ketamine (cumulative dose-response curve) and addition of isoproterenol. At the end of each experiment, the muscle length at L_{max} was measured using Vernier calipers. The muscle was

Table 2. Baseline Contractile Variables at L_{max}

Variable	Nonfailing Atrial Muscle (n = 66 from 14 hearts)	Failing Atrial Muscle (n = 16 from 4 hearts)	Failing Ventricular Muscle (n = 26 from 9 hearts)
Resting tension (mN/mm^2)	25 ± 3	25 ± 6	34 ± 1
Developed tension (mN/mm^2)	20 ± 3	12 ± 2*	17 ± 6
Time to peak tension (msec)	75 ± 5	76 ± 10	160 ± 9
Time to half relaxation (msec)	82 ± 3	77 ± 6	144 ± 5
Maximal rate of tension rise (mN/mm^2/sec)	165 ± 14	174 ± 16	91 ± 4
Maximal rate of tension fall (mN/mm^2/sec)	87 ± 7	106 ± 6	72 ± 2

Values are mean ± SEM.

* $P < 0.05$ nonfailing *versus* failing atrial muscles. Statistical comparisons were made only between failing and nonfailing atrial muscles.

weighed, and the cross-sectional area was calculated by dividing the muscle weight by the length and multiplying by density, assuming a cylindrical shape and a tissue density of 1.0 mg/mm^3.[16] To minimize differences resulting from muscle size alone, the cross-sectional area of the muscle was used to normalize the values of resting tension, DT, and ±dT/dt for all muscles. Average peak DT at L_{max} in the three muscle groups was compared with preoperative ejection fraction measured in the patients before surgery.

Statistical Analysis

Contractile parameters for atrial and ventricular muscles taken from the same heart were averaged, such that each heart was used as a single observation and contributed only once to the overall data set. Responses to ketamine and buffer (in vehicle control muscles) were compared using repeated-measures analysis of variance (analysis of variance with Student-Newman-Keuls testing for individual paired doses) for each of the six contractile variables within each group of muscles. Repeated-measures analysis of variance also was used to compare the dose–response curve between the nonfailing and failing atrial muscles. Atrial and ventricular muscles were not compared. Spearman's correlation coefficient was used to compare the maximum DT at L_{max} (*in vitro*) with the preoperative ejection fraction (*in vivo*). For this analysis, the DT of all individual muscles (n = 108) was correlated to the respective preoperative ejection fraction. All values are given as mean ± SEM. Actual statistical differences were quoted, but the accepted level of significance was $P < 0.05$.

Results

Table 1 shows the patients' demographic data, preoperative medications, anesthetic agents and drugs used before and during surgery, and preoperative left ventricular ejection fraction. Table 2 shows baseline contractile variables recorded at L_{max} from all human atrial and ventricular muscles used. The L_{max} in failing atrial muscle was lower than that in nonfailing atrial muscle ($P < 0.02$). Because nonfailing ventricular muscle was not available, we were unable to compare the contractile properties of failing ventricle at L_{max} with nonfailing controls. *In vivo* ejection fractions correlated positively with the corresponding maximum developed tension at L_{max} ($r = 0.27$, $P < 0.005$, $n = 108$).

Effects of Ketamine on Developed Tension in Nonfailing and Failing Hearts

Figure 1 shows a representative tracing of the dose–response curve to ketamine for DT in nonfailing (top) and failing (bottom) atrial muscles. In nonfailing atrial trabecular muscle, ketamine caused a dose-dependent decrease in DT starting at a dose of 88 μM ($P < 0.01$; fig. 2, top). The maximal decrease in DT (to 23 ± 4% of baseline) was found at the highest, supratherapeutic, ketamine concentration (440 μM). Isoproterenol returned the DT toward the baseline value, although DT was still only 66 ± 7% of baseline ($P > 0.05$). Ketamine caused a large dose-dependent decrease ($P < 0.001$) in DT in failing atrial muscles starting at 264 μM and in ventricular muscles starting at 44 μM (fig. 2, bottom). At a supraphysiologic ketamine dose of 440 μM, DT was 17 ± 4% and 11 ± 5% of baseline for failing atrial and ventricular muscles, respectively, and treatment with

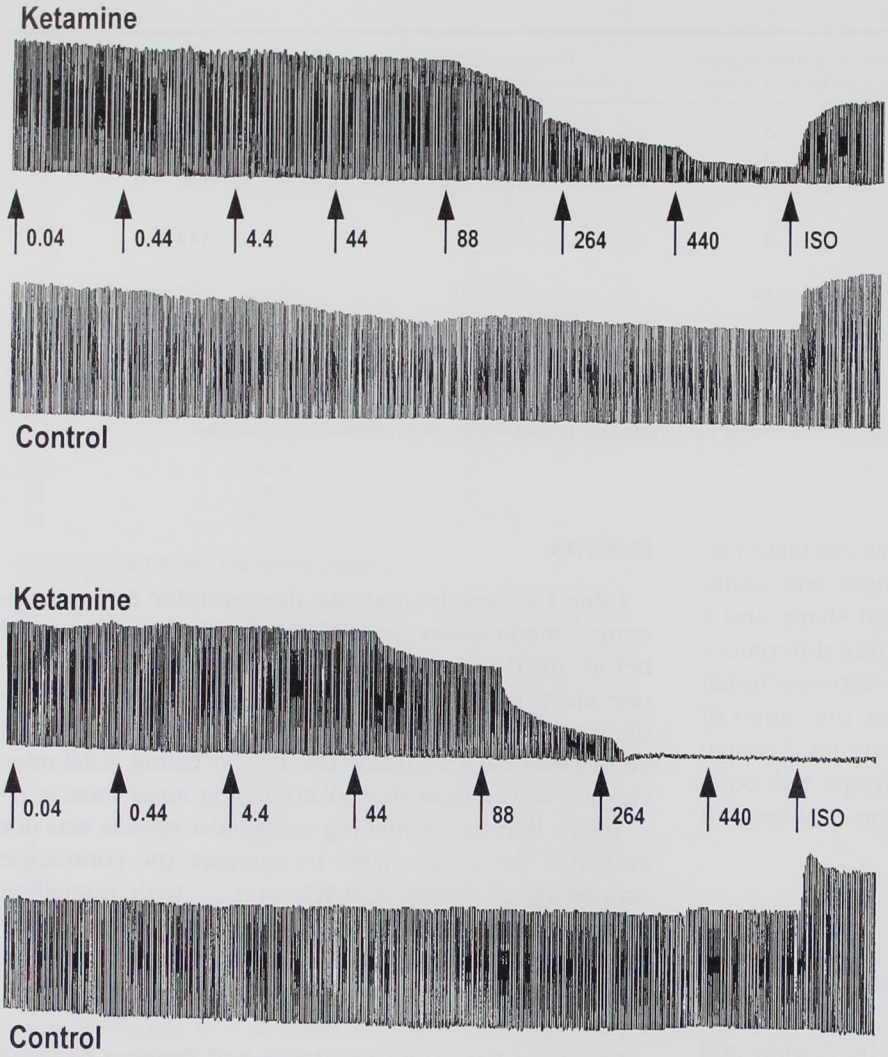

Fig. 1. A representative tracing of the developed tension dose–response curve to ketamine in nonfailing (*top*) and failing (*bottom*) atrial muscles. The dose of ketamine was added in increments from 0.04 to 440.0 μM. ISO = 1 μM isoproterenol.

isoproterenol did not reverse the decrease in DT ($P > 0.05$) in either case. In all vehicle-treated control muscles (failing and nonfailing), isoproterenol increased DT to 136% of baseline in nonfailing atrium and to 176% and 178% in failing atrium and ventricle, respectively ($P < 0.01$ for all).

Effects of Ketamine on Other Contractility Variables

Figures 3 and 4 show changes in +dT/dt and −dT/dt (relative to that developed at baseline) in the nonfailing atrial and failing atrial and ventricular muscles after treatment with ketamine and isoproterenol compared with vehicle control. These changes in contractility paralleled those in maximum DT. There were no significant effects of ketamine on resting tension, time to peak tension, or time to half relaxation in any group of muscles studied ($P > 0.05$).

Discussion

The preserved hemodynamic response to ketamine has been attributed to its central and peripheral sympathomimetic action *via* blockade of norepinephrine reuptake in adrenergic nerves.[17] When the sympathetic tone is abolished, however, such as occurs during general anesthesia with halothane and enflurane[11] or during epidural anesthesia,[18] ketamine produces no pressor response. The observation that ketamine can lead to a

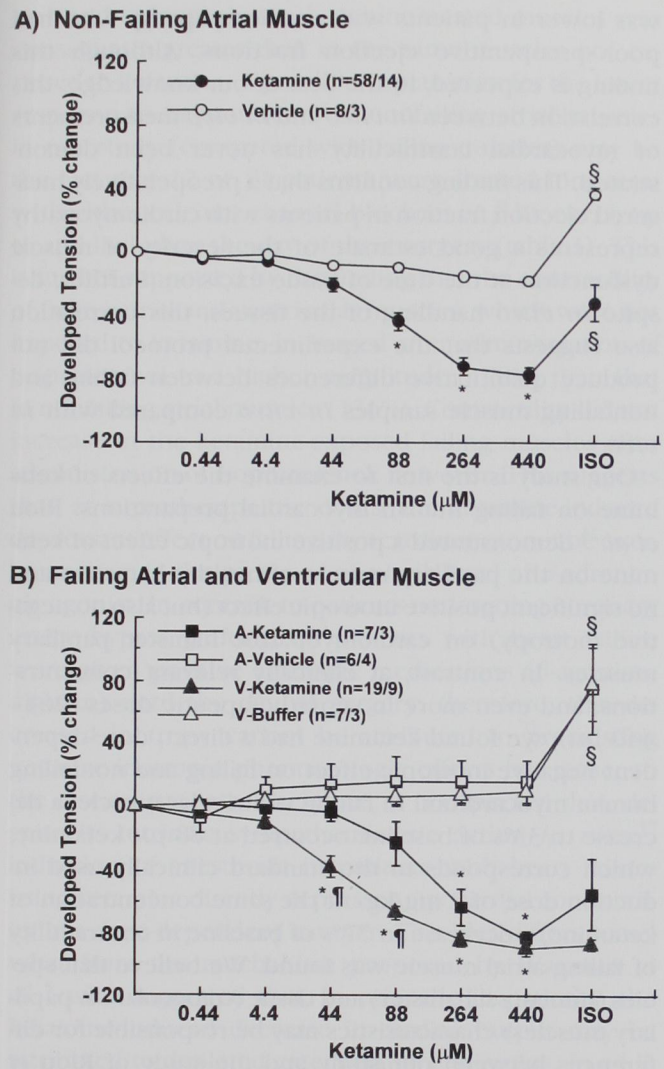

Fig. 2. Effects of ketamine on developed tension in nonfailing atrial muscle (*A*) and in failing atrial and ventricular muscle (*B*). Data are expressed as mean ± SEM. **P* < 0.05 *versus* vehicle control; ¶*P* < 0.05 *versus* A-Ketamine; §*P* < 0.05 *versus* preceding dose. n = no. of muscles/no. of hearts; ISO = 1 μM isoproterenol.

cardiodepressant action in a subset of critically ill[5] and anesthetized[11] patients has stimulated exploration of its direct effects on cardiovascular function. This paradoxical response to ketamine in such patients has been attributed to absent or attenuated central and peripheral adrenergic transmission, leaving the myocardium exposed to the direct depressant effect of ketamine.[19]

Most *in vitro* studies have found that ketamine has negative inotropic characteristics,[6–8] but this conclusion remains controversial because ketamine also appears to exert biphasic effects (low-dose positive inotropy, high-dose negative inotropy)[20,21] or direct positive inotropic effects.[9,10,22] At identical concentrations of ketamine (3×10^{-4} M), Endou *et al.*[21] determined that contractile force decreased 19% in guinea pig papillary muscles and increased 178% in rat left atria; they postulated that whether ketamine has positive or negative inotropic effects depends entirely on the species and cardiac tissue studied. Therefore, although the most common finding *in vitro* is that ketamine produces direct negative inotropic effects when the competing actions of centrally mediated or direct peripheral sym-

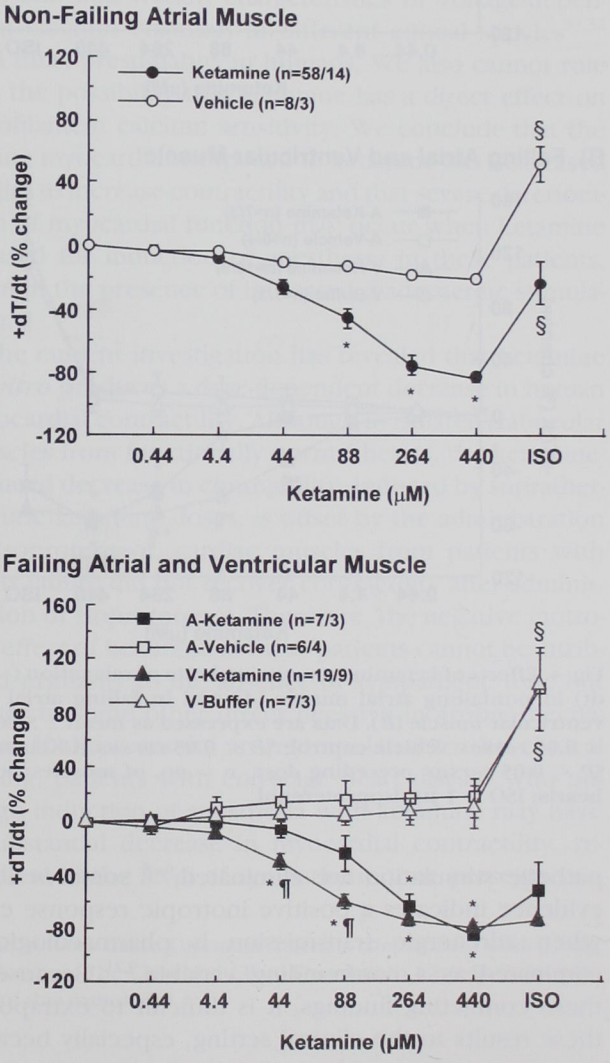

Fig. 3. Effects of ketamine on maximal rate of contraction (+dT/dt) in nonfailing atrial muscle (*A*) and in failing atrial and ventricular muscles (*B*). Data are expressed as mean ± SEM. **P* < 0.05 *versus* vehicle control; ¶*P* < 0.05 *versus* A-Ketamine; §*P* < 0.05 *versus* preceding dose. n = no. of muscles/no. of hearts; ISO = 1 μM isoproterenol.

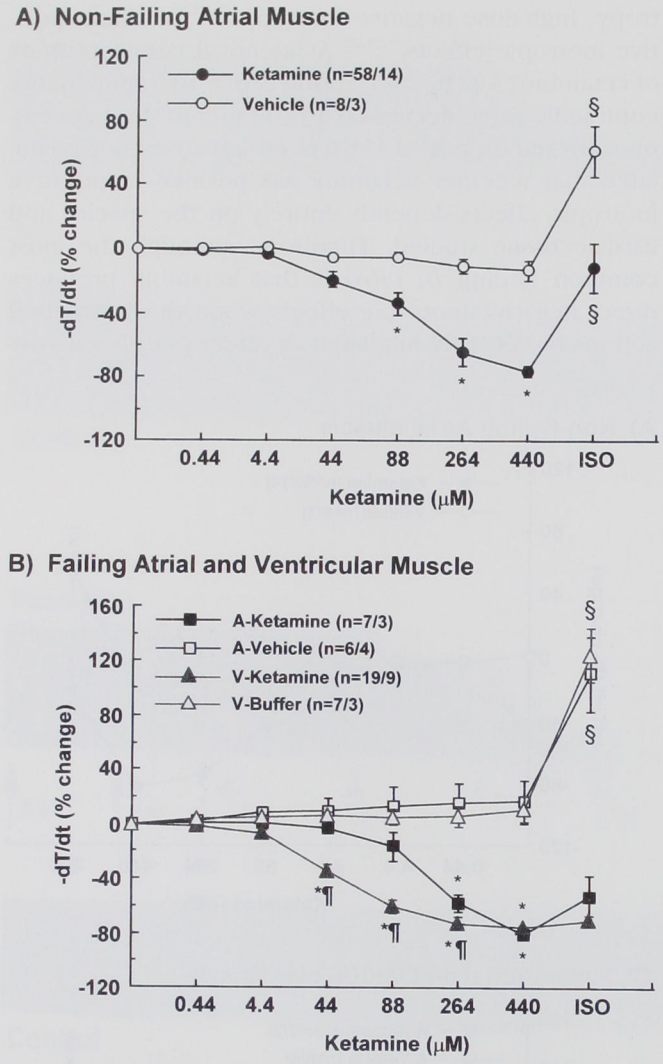

Fig. 4. Effects of ketamine on maximal rate of relaxation (−dT/dt) in nonfailing atrial muscle (*A*) and in failing atrial and ventricular muscle (*B*). Data are expressed as mean ± SEM. **P* < 0.05 *versus* vehicle control; ¶*P* < 0.05 *versus* A-Ketamine; §*P* < 0.05 *versus* preceding dose. n = no. of muscles/no. of hearts; ISO = 1 μM isoproterenol.

pathetic stimulation are eliminated,[6–8] some *in vitro* evidence indicates a positive inotropic response even when adrenergic transmission is pharmacologically eliminated as a confounding variable.[9,21] Because of these conflicting findings, it is difficult to extrapolate these results to the clinical setting, especially because the direct effects of ketamine on human myocardial cells are unknown. Therefore, we deemed it important to study the effect of ketamine on human myocardium.

We found that *in vitro* myocardial contractility correlated well with *in vivo* contractility; maximal DT at L_{max} was lower in patients with cardiomyopathy who had poor preoperative ejection fractions. Although this finding is expected, to the best of our knowledge, this correlation between *in vitro* and *in vivo* measurements of myocardial contractility has never been demonstrated. This finding confirms that a preoperatively measured ejection fraction in patients with cardiomyopathy represents a good estimate of the severity of muscle dysfunction at the time of tissue excision. Further, despite *in vitro* handling of the tissues, this correlation also suggests that the experimental protocol did not produce quantitative differences between failing and nonfailing muscle samples *in vitro* compared with *in vivo*.

Our study is the first to examine the effects of ketamine on failing human myocardial preparations. Riou *et al.*[23] demonstrated a positive inotropic effect of ketamine on the papillary muscle of healthy hamsters and no significant positive inotropic effect (but also no negative inotropy) on cardiomyopathic hamster papillary muscles. In contrast, at clinically relevant concentrations, and even more in supratherapeutic doses (264–440 μM), we found ketamine had a direct, dose-dependent negative inotropic effect on failing and nonfailing human myocardium. In failing ventricular muscle, a decrease to 33% of baseline occurred at 88 μM ketamine, which corresponds to the standard clinically used induction dose of 2 mg/kg. At the same concentration of ketamine, a decrease to 77% of baseline in contractility of failing atrial muscle was found. We believe that species (human *vs.* hamster) and tissue (trabecular *vs.* papillary muscles) characteristics may be responsible for differences between our study and the study of Riou *et al.*,[23] because in other studies a positive inotropic response to ketamine has been demonstrated repeatedly in rat papillary muscles.[22] In addition, there are substantial methodologic differences between the two studies. Our experiments were performed at 37°C, whereas theirs were done at 29°C. Further, the rate of stimulation in our study was 60/min, and Riou *et al.*[23] stimulated their hamster muscles at 0.12 Hz (7/min). In the nonfailing muscles used in our study, even after a supratherapeutic dose of ketamine, the decrease in myocardial contractility was restored toward the baseline value with a single dose of isoproterenol (1 μM isoproterenol has been shown to produce a maximal inotropic effect in human trabecular muscle),[14,15] but DT did not exceed the pretreatment baseline values. This is contrary to the findings of Adams *et al.*[24] on guinea pig atria, who determined that the inotropic response to norepineph-

rine and epinephrine in ketamine-treated muscles was consistently greater than in the same muscles not exposed to ketamine. A possible explanation for the lower response to isoproterenol in nonfailing atrial muscles in our study (compared with failing muscles) may be the fact that 12 of 14 patients were treated long-term with either calcium channel blockers or β-blockers, up to and including the day of their surgery (table 1). This is further supported by the finding that the contractility of failing atrial and ventricular muscles, which were not exposed to ketamine, increased after administration of isoproterenol to a higher magnitude (178%) than that in nonfailing atrial muscles (136%). Contractility did not increase in the ketamine-exposed failing muscles after administration of isoproterenol, however. This suggests that, at supratherapeutic doses, the ketamine-induced depressant effect on failing myocardium cannot be overcome even in the presence of a high level of β-adrenergic agonist. In contrast to patients undergoing coronary artery bypass grafting, all patients with heart failure were given positive inotropic medications (β-agonists, digoxin) until the day of surgery; therefore, this decreased inotropy cannot be attributed to preexisting negative inotropic pharmacologic effects but rather to the disease process. Therefore, it is expected that, despite its intrinsic sympathomimetic action *in vivo,*[17] induction of anesthesia in patients with heart failure using ketamine directly depresses myocardial contractility in a dose-dependent manner. This idea differs somewhat from the mechanism proposed by Waxman *et al.,*[5] who suggested that, in critically ill patients, the ketamine-induced decrease in cardiac output may be attributed to depleted catecholamine stimulus. In addition, the level of sympathetic tone and its effects on the myocardium may be different between patients with end-stage heart disease, such as ours, and the patients described by Waxman *et al.*[5] Concentration of norepinephrine in plasma are increased in the long-term in patients with end-stage heart failure.[25] It has been shown that the number of β-receptors and the β-adrenoceptor-mediated inotropic response is decreased by 50-60% in failing hearts.[26,27] Therefore, in chronic heart failure, the pathogenesis of decreased responsiveness to catecholamines has been attributed primarily to endogenous receptor downregulation.[28] In contrast, in acutely ill patients, myocardial responsiveness to catecholamines still may be preserved. That this response to isoproterenol was completely abolished in the presence of a supratherapeutic dose of ketamine supports the hypothesis that mechanisms other than β-receptor downregulation[26,27] or the absence of sympathetic tone[5] are responsible for the effects of ketamine on contractility in failing myocardium. Other mechanisms may involve the direct action of ketamine on calcium ionic flux. Baum *et al.*[29] and Rusy *et al.*[30] found that, at clinically relevant concentrations, ketamine directly inhibits transsarcolemmal calcium influx in guinea pig and rabbit papillary muscles but has relatively little effect on the availability of calcium stored in or released from the sarcoplasmic reticulum.[30] Ketamine may decrease cardiac function at least in part by inducing changes in the voltage-dependent activation and inactivation characteristics of voltage-dependent calcium channels in different animal species[31,32] and thus, presumably, in humans. We also cannot rule out the possibility that ketamine has a direct effect on myofilament calcium sensitivity. We conclude that the failing myocardium exposed to ketamine has decreased ability to increase contractility and that severe deterioration of myocardial function may occur when ketamine is used for induction of anesthesia in these patients, even in the presence of increased β-adrenergic stimulation.

The current investigation has revealed that ketamine *in vitro* produces a dose-dependent decrease in human myocardial contractility. Although in isolated trabecular muscles from functionally normal hearts, the ketamine-induced decrease in contractility, induced by supratherapeutic ketamine doses, is offset by the administration of isoproterenol, cardiac muscles from patients with heart failure did not recover contractility after administration of isoproterenol. Therefore, the negative inotropic effect of ketamine in these patients cannot be attributed primarily to the absence of sympathetic tone but rather to some other direct negative inotropic mechanism. If these results are extrapolated to the clinical setting, patients with end-stage heart disease who undergo induction of anesthesia with ketamine may have a substantial decrease in myocardial contractility, regardless of the level of sympathetic tone present.

The authors thank Cassandra Talerico (Department of Scientific Publications, The Cleveland Clinic Foundation) for help in preparation of this manuscript.

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