

# Inotropic Effect of Ketamine on Rat Cardiac Papillary Muscle

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The direct effect of ketamine on cardiac muscle was studied using rat left ventricular papillary muscle. At an extracellular calcium concentration ( $[Ca^{++}]_0$ ) of 2.5 mM, rat myocardial contractility is nearly maximum, and a positive inotropic effect was demonstrated by an increase in maximum shortening velocity ( $V_{max}$ ) with ketamine at  $10^{-5}$  M but not  $10^{-4}$  M. At a  $[Ca^{++}]_0$  of 0.5 mM, ketamine  $10^{-5}$  and  $10^{-4}$  M had a positive inotropic effect as shown by an increase in  $V_{max}$  ( $135\% \pm 22\%$  and  $147\% \pm 33\%$ , respectively) and in isometric active force (AF/s) ( $120\% \pm 10\%$  and  $152\% \pm 44\%$ , respectively). The positive inotropic effect of ketamine was not related to catecholamine uptake inhibition and/or  $\alpha/\beta$  receptor stimulation because it persisted after phentolamine and propranolol and because ketamine had no relaxing effect. Ketamine  $10^{-5}$  and  $10^{-4}$  M impaired isotonic relaxation, contraction-relaxation coupling under low loading conditions, and the load sensitivity of relaxation, which suggests impairment of the calcium sequestering systems, especially the sarcoplasmic reticulum (SR). Ketamine modified postrest recovery: the first beat (B1) after a 1-min rest period was decreased by ketamine  $10^{-4}$  M but not ketamine  $10^{-5}$  M. Moreover, the beat-to-beat postrest recovery has been demonstrated to be exponential, and  $\tau$ , the time constant of the decay was increased by ketamine  $10^{-4}$  M ( $5.4 \pm 0.3$  vs.  $3.9 \pm 0.2$  beats) but not by ketamine  $10^{-5}$  M ( $3.4 \pm 0.4$  vs.  $3.7 \pm 0.2$  beats). These effects on postrest recovery suggest that ketamine impairs SR function. The authors suggest that ketamine had a dual action on rat myocardium: a positive inotropic effect without any relaxing effect, probably related to an increase in calcium influx, and an impairment of SR function. Nevertheless, impairment of SR is only significant at high concentration ( $10^{-4}$  M) and might overcome the positive inotropic effect only at supratherapeutic concentration. (Key words: Anesthetics, intravenous: ketamine. Heart, papillary muscle: contractility.)

KETAMINE is a short-acting iv anesthetic, which has been shown to produce a marked increase in arterial blood pressure, heart rate, and cardiac output.<sup>1</sup> Cardiovascular stimulation associated with ketamine administration is thought to be due to sympathomimetic effects mediated within CNS structures,<sup>2</sup> inhibition of intraneuronal uptake

of catecholamines (cocaine-like effect on postganglionic adrenergic neurons) and inhibition of extraneuronal norepinephrine uptake.<sup>3</sup> Critically ill patients may respond to ketamine with an unexpected decrease in blood pressure,<sup>4</sup> which is thought to result from the inability of sympathomimetic actions of ketamine to counterbalance its direct vasodilatory and myocardial depressant effects.<sup>4,5</sup> It is thus of interest to determine whether ketamine is actually a direct myocardial depressant.

The myocardial effects of ketamine remain controversial. *In vivo* in the absence of autonomic control, it has been suggested that ketamine has direct myocardial depressant properties.<sup>6</sup> However, because of simultaneous changes in preload, systemic resistance, baroreflex activity, and CNS activity, the precise *in vivo* effects of an anesthetic agent on myocardial contractility are difficult to assess.<sup>7</sup> *In vitro* ketamine has been reported to be both a negative<sup>8</sup> or a positive inotropic agent.<sup>9</sup> Most studies that demonstrated a negative inotropic effect of ketamine tested high concentrations of ketamine (greater than  $10^{-4}$  M). When testing lower concentrations, no changes in the strength of contraction have been observed in rat cardiac papillary muscle,<sup>8</sup> but this study has been performed with an extracellular calcium concentration ( $[Ca^{++}]_0$ ) of 2.5 mM, and contractility levels of rat myocardium are nearly maximum at this concentration.<sup>10</sup>

We conducted an *in vitro* study on the effects of ketamine on rat cardiac papillary muscle. The experimental model used in the present study enabled us to determine the effects of ketamine on cardiac muscle more accurately than simply the direction and magnitude of the change produced in the strength of contraction, *i.e.*, changes in the fundamental intrinsic mechanical properties of cardiac muscle.

## Materials and Methods

### EXPERIMENTAL PROTOCOL

Forty left ventricular papillary muscles of adult male Wistar rats (weighing 340–400 g) were used in this study. Care of the animals conformed to the recommendations from the Declaration of Helsinki, and the study was authorized by our institution (INSERM). After brief anesthesia with ether, hearts were quickly removed and papillary muscles were carefully excised and suspended vertically in 60 ml Krebs-Henseleit bicarbonate buffer solution containing (in mM) 118 NaCl, 4.7 KCl, 1.2  $MgSO_4 \cdot 7H_2O$ , 1.1  $KH_2PO_4$ , 25  $NaHCO_3$ , 2.5  $CaCl_2 \cdot 6H_2O$ , and 4.5 glucose. The preparations were field stim-

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TABLE 1. Papillary Muscle Characteristics during Control Conditions at  $L_{max}$  and at a  $[Ca^{++}]_0$  of 2.5 mM in Groups 1-5

|                    | $L_{max}$ (mm)         | $s$ (mm <sup>2</sup> )     | RF/TF                      | R1                         | Isot A/Isom A              |
|--------------------|------------------------|----------------------------|----------------------------|----------------------------|----------------------------|
| Group 1<br>(n = 8) | 5.7 ± 0.5<br>(5.0-6.0) | 0.80 ± 0.16<br>(0.64-1.18) | 0.14 ± 0.05<br>(0.10-0.27) | 0.71 ± 0.09<br>(0.59-0.83) | 0.80 ± 0.02<br>(0.71-0.85) |
| Group 2<br>(n = 8) | 5.5 ± 1.3<br>(4.0-7.0) | 0.72 ± 0.14<br>(0.57-0.93) | 0.13 ± 0.03<br>(0.10-0.18) | 0.68 ± 0.10<br>(0.60-0.84) | 0.80 ± 0.03<br>(0.70-0.82) |
| Group 3<br>(n = 8) | 5.7 ± 1.3<br>(4.0-7.0) | 0.92 ± 0.22<br>(0.54-1.20) | 0.17 ± 0.03<br>(0.13-0.23) | 0.73 ± 0.10<br>(0.48-0.84) | 0.72 ± 0.05<br>(0.64-0.79) |
| Group 4<br>(n = 8) | 5.4 ± 1.1<br>(4.0-7.0) | 0.67 ± 0.23<br>(0.54-1.08) | 0.16 ± 0.04<br>(0.10-0.23) | 0.62 ± 0.13<br>(0.48-0.82) | 0.76 ± 0.05<br>(0.65-0.80) |
| Group 5<br>(n = 8) | 5.7 ± 0.6<br>(4.5-6.0) | 1.05 ± 0.12<br>(0.90-1.20) | 0.14 ± 0.05<br>(0.09-0.22) | 0.75 ± 0.07<br>(0.68-0.85) | 0.72 ± 0.05<br>(0.65-0.78) |

Values are mean ± SD; ranges are given in parentheses.  $s$  = cross-sectional area; RF/TF = ratio of resting force to total force; R1 = ratio of maximum isotonic shortening velocity to maximum lengthening

velocity; Isot A/Isom A = index of load sensitivity of relaxation (fig. 1). Analysis of variance: no differences between groups.

ulated at 0.12 Hz by two platinum electrodes with rectangular wave pulses of 5 ms duration just above threshold. The bathing solution was bubbled with 95% O<sub>2</sub>/5% CO<sub>2</sub>, resulting in a pH of 7.40, and was kept constant at 29° C. After a 1-h stabilization period at  $L_{max}$  (*i.e.*, the initial muscle length at the apex of the length-active isometric tension curve), papillary muscles recovered their optimal mechanical performance, which are stable for many hours. Suitable preparations were selected on the basis of the following criteria: length at  $L_{max}$  ≥ 3.5 mm, cross-sectional area ≤ 1.20 mm<sup>2</sup>, ratio of resting force to total isometric force (RF/TF) ≤ 0.30, R1 ≤ 0.85 (R1 is the ratio between isotonic shortening and lengthening velocities at a load equal only to the preload for  $L_{max}$ ), and Isot A/Isom A ≤ 0.85 (Isot A/Isom A is the ratio between two areas under a specific set of isotonic and isometric force *vs.* time) (fig. 1) and tests load sensitivity of relaxation. These two last parameters (R1 and Isot A/Isom A) were chosen because they are sensitive to core hypoxia and to careless excision. Table 1 summarizes the muscle characteristics during control conditions at  $L_{max}$ .

Control values of each mechanical parameter were recorded, and ketamine hydrochloride (Ketalar, Substantia) was then added to the bathing solution. Rat papillary muscles were divided into five groups. In group 1 (n = 8) ketamine 10<sup>-4</sup> M corresponding to peak serum concentrations obtained during induction of anesthesia<sup>11</sup> was tested at a  $[Ca^{++}]_0$  of 2.5 mM. In group 2 (n = 8) ketamine 10<sup>-5</sup> M corresponding to serum concentrations of ketamine obtained during maintenance of anesthesia<sup>11</sup> was tested at a  $[Ca^{++}]_0$  of 2.5 mM. In groups 3 (n = 8) and 4 (n = 8),  $[Ca^{++}]_0$  was decreased from 2.5 to 0.5 mM, and then ketamine 10<sup>-4</sup> M (group 3) or 10<sup>-5</sup> M (group 4) was added to the bathing solution.  $[Ca^{++}]_0$  was decreased for the following reasons: 1) because rat myocardial contractility is nearly maximum at 2.5 mM of  $[Ca^{++}]_0$ , it is difficult to exhibit and therefore to quantify a positive inotropic

effect without decreasing  $[Ca^{++}]_0$  to 0.5 mM<sup>12</sup>; and 2) a postrest contraction study is easier to conduct in rat at a low  $[Ca^{++}]_0$ .<sup>13</sup> In group 5 (n = 8) phentolamine 10<sup>-6</sup> M (Regitine, Ciba-Geigy) and propranolol 10<sup>-6</sup> M (Avlocardyl, ICI Pharma) were added before ketamine 10<sup>-4</sup> M at a  $[Ca^{++}]_0$  of 0.5 mM to block both  $\alpha$  and  $\beta$  adrenergic receptors.

Changes in mechanical parameters were studied up to 60 min following ketamine administration to the bathing solution because a preliminary study showed that effects of ketamine remained stable for 45-60 min.

#### ELECTROMAGNETIC LEVER SYSTEM

The electromagnetic lever system has been previously described.<sup>14</sup> Briefly, the load applied to the muscle was determined by a servocontrolled current through the coil of an electromagnet. Muscular shortening induced a displacement of the lever, which modulated the light intensity of a photoelectric transducer. The system had a linear range up to 2.5 mm of muscle shortening (resolution 0.25  $\mu$ m). The force measurement amplitude ranged from 0 to 100 millinewtons (mN) (resolution < 0.1 mN). The equivalent moving mass of the whole system was 155 mg, and the compliance was 0.2  $\mu$ m/mN.

#### RECORDING

All analyses were made from digital records obtained with a Hewlett Packard 1000 computer. The records were stored on a hard disk (60 Mo). Two signals were recorded: force and length. The recording speed was one A/D conversion of each signal every 1 ms. A single recording had 500 points for each signal, for a total recording time of 500 ms. A program was designed in our laboratory to calculate all mechanical parameters and was extensively tested and demonstrated to be accurate and error-free. For the figures, muscle force and length were displayed

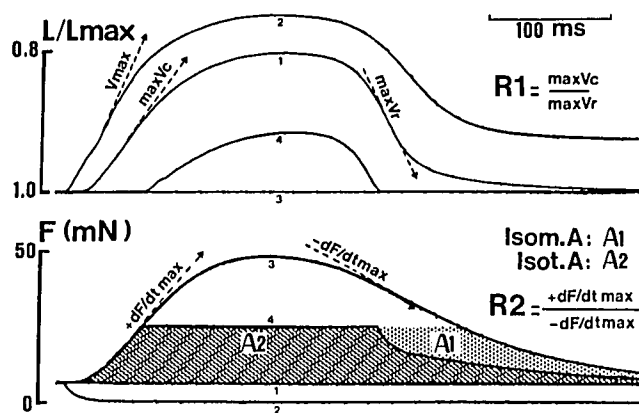


FIG. 1. Mechanical parameters of contraction and relaxation. *Upper graph:* muscle shortening length ( $L/L_{max}$ ) was plotted *versus* time. *Lower graph:* force ( $F$ ) was plotted *versus* time. Twitch 1 was loaded with preload only at  $L_{max}$ . Twitch 2 was loaded with same preload as twitch 1 and was abruptly clamped to zero load with critical damping just after stimulation. Twitch 3 was fully isometric and twitch 4 was loaded at 50% of isometric active force. The index used to quantify the load sensitivity of relaxation was the ratio of two areas: the areas Isot A and Isom A were limited by force *versus* time curves of twitch 4 and 3, respectively, and below 50% of active force level. The isometric area (A1) includes the isotonic area (A2). This index approaches 1 when load sensitivity disappears.

on a storage display unit (Tektronix 611) and recorded on hard copy (Tektronix 4601).

#### MECHANICAL PARAMETERS

Conventional mechanical parameters at  $L_{max}$  were calculated from four twitches. The first twitch was isotonic and was loaded with the preload only at  $L_{max}$ . The second twitch was abruptly clamped to zero-load just after the electrical stimulus (<3 ms); the maximum unloaded shortening velocity ( $V_{max}$ ) was determined from this twitch. The third twitch was fully isometric at  $L_{max}$ . The fourth twitch was isotonic and was afterloaded to half-value of the isometric active force at  $L_{max}$ . Detailed explanations and definitions of mechanical indices for the various phases of contraction are given in figure 1.

The mechanical parameters characterizing contraction and relaxation phases, coupling between contraction and relaxation, and the load sensitivity of relaxation are defined as follows:

##### Contraction Phase

Maximum unloaded shortening velocity ( $V_{max}$ ) by means of the zero-load clamp technique<sup>15</sup>; maximum shortening velocity ( $maxVc$ ) of the twitch with preload only; maximum isometric active force normalized per cross-sectional area ( $AF/s$ ); peak of the positive force derivative normalized per cross-sectional area ( $+dF/dt_{max}/s$ ); time-to-peak force (TPF) of the isometric twitch; time-

to-peak shortening (TPS) of the isotonic twitch with preload only. The maximum shortening velocity ( $V_{max}$ ) and the maximum isometric force ( $AF/s$ ) tested the inotropic state of papillary muscle under low and heavy loading conditions, respectively.

##### Relaxation Phase

Maximum lengthening velocity of the twitch with preload only ( $maxVr$ ), and the peak of the negative force derivative at  $L_{max}$  normalized per cross-sectional area ( $-dF/dt_{max}/s$ ). Relaxation is an important phase in cardiac mechanics. The main intrinsic determinants of heart work are heart rate, inotropic state, and lusitropic state.<sup>16</sup> Inotropy characterizes the contraction phase and lusitropy the relaxation phase, and altered lusitropy influences ventricular pressure-volume loops.<sup>16</sup> The two parameters,  $maxVr$  and  $-dF/dt_{max}/s$ , tested the lusitropic state of papillary muscle under low and heavy loading conditions, respectively. However, because relaxation depends on the degree of contraction, simultaneous variations of contraction and relaxation must be considered to quantify the drug-induced changes in relaxation. Therefore, indices that test the contraction-relaxation coupling have been developed.<sup>17</sup>

##### Contraction-Relaxation Coupling

Coefficient  $R1 = maxVc/maxVr$  tests the coupling between contraction and relaxation under low loading conditions; coefficient  $R2 = (+dF \cdot dt^{-1}max)/(-dF \cdot dt^{-1}max)$ , tests the coupling between contraction and relaxation under heavy loading conditions. The regulation of the time course of relaxation depends on loading conditions. Various factors, especially sarcomere length, have been considered to modulate the calcium sensitivity of myofilaments and, consequently, the relaxation. In isotonic conditions the amplitude of sarcomere shortening is about twice that observed in isometric conditions,<sup>18</sup> and isotonic relaxation occurred more rapidly than isometric relaxation partly due to two mechanisms<sup>19</sup>: 1) the easier removal of calcium from troponin C due to the decrease of calcium sensitivity of myofilaments at shorter sarcomere lengths; and 2) the rapid calcium uptake by the sarcoplasmic reticulum (SR). Under low loading conditions and/or short sarcomere lengths, the SR appears to play a major role in the regulation of the time course of isotonic relaxation because calcium can quickly dissociate from troponin C.<sup>17,20</sup> Under heavy loading conditions, the amplitude of sarcomere shortening is reduced, the sensitivity of myofilaments to calcium is higher and become therefore the limiting step, and appears to play a major role in the regulation of the time course of isometric relaxation.

### Load Sensitivity of Relaxation

The concept of load sensitivity reflects the capacity of mammalian heart muscle to accurately regulate the time course of relaxation according to loading conditions. In a typical load-sensitive papillary muscle (fig. 1), isometric relaxation of an afterloaded twitch occurs earlier compared with the superimposed force trace of the fully isometric twitch. In a load-insensitive muscle, superimposed isometric relaxation coincides in time irrespective to the load applied during the contraction phase. The ratio of two areas (Isot A/Isom A) (fig. 1) has been proposed to quantify the degree of load sensitivity of cardiac muscle.<sup>14,17</sup> This ratio ranges from about 0.75 in a typical load-sensitive relaxation to 1 in a typical load-insensitive relaxation and provides a precise scale of measurement for load sensitivity. Load dependence of mammalian cardiac muscle is thought to reflect the presence of effective calcium sequestering systems, particularly the sarcoplasmic reticulum. A decrease in load sensitivity of relaxation can result from an abbreviation of isometric relaxation, from a slowing of isotonic relaxation, or from both. During hypoxia cardiac mammalian muscle become load-insensitive because of abbreviation of isometric relaxation (due to a reduced sensitivity of myofilaments to calcium) and slowing of isotonic relaxation (due to a decrease in rate of calcium uptake by the SR).<sup>20</sup> However, a drug-induced decrease in load sensitivity is more frequently only due to a slowing of isotonic relaxation related to a decrease in calcium uptake by the SR.

Shortening and lengthening velocities were expressed in  $L_{\max} \cdot s^{-1}$ , force in  $mN \cdot mm^{-2}$ , force derivative in  $mN \cdot s^{-1} \cdot mm^{-2}$ , time in ms.

### POSTREST CONTRACTION

Recovery of a stable, reproducible isometric contraction after a 1-min rest interval was studied to identify the effects of ketamine on both sources of myofibrillar activating calcium: sarcolemma and SR. In rat myocardium the major source of calcium that activates myofilaments is the SR.<sup>10,13</sup> During rest in the rat, the SR accumulates additional calcium above and beyond that accumulated with regular stimulation, and the first beat after the rest interval (B1) is more forceful than the beat before the rest interval (B0).<sup>13,21</sup> During the stimulation of the postrest recovery (B<sub>2</sub>, B<sub>3</sub>), the SR derived portion of activator calcium decreases somewhat toward a steady state, which is reached in a few beats. The transsarcolemmic derived fraction of activator calcium progressively increases a small amount, although it remains a small portion of total activating calcium. Therefore, the effects of ketamine on postrest potentiated contraction may suggest effects upon the SR and provide additional details in a biochemically unaltered preparation regarding ketamine interactions with the SR.

A 1-min rest duration was used because postrest recovery remains stable as rest duration varies from 30 s to 3 min in the rat myocardium.<sup>13</sup> Because the ratio B1/B0 can be increased by lowering  $[Ca^{++}]_0$ , postrest recovery was studied at a  $[Ca^{++}]_0$  of 0.5 mM.

The beat-to-beat decay of the potentiated contraction has been demonstrated to be exponential.<sup>21</sup> The beat-to-beat decay of mean AF/s (y) during postrest recovery was plotted against the number of beat (n) and fitted to an exponential curve according to equation 1:

$$y = a \times 10^{-bn} \quad (1)$$

Because of the uncertainty in measurement when the ratio Bn/Bo was below 1%, the beat Bn and subsequent beats were not considered for regression analysis. The rate constant,  $\tau$ , of the exponential decay of mean AF/s, was derived from b according to equation 2:

$$\tau = b^{-1} \quad (2)$$

According to equations 1 and 2,  $\tau$  is the number of beats required for the postrest contraction to decay to  $1/10$  of its maximum (B1),  $\tau$  is beat dependent but does not change with stimulation frequency,<sup>21</sup> and consequently is not really "time dependent."  $\tau$  also depends on  $[Ca^{++}]_0$  but not on initial length and has been assumed to represent the time required for the SR to reset itself, and therefore to test SR function.<sup>21</sup>

### STATISTICAL ANALYSIS

Data were expressed as mean  $\pm$  SD (text and tables) or  $\pm$ SEM (figures). Comparisons with control values were performed using the paired Student's *t* test. Comparison between groups was performed using Student's *t* test or analysis of variance whenever appropriate. Regression analysis was performed using the least squares method. Comparison of the slope of the regression curve was performed using Student's *t* test. All *P* values were two-tailed and a *P* value  $< 0.05$  was necessary to reject the null hypothesis.

### Results

There were no statistically significant differences between control values for  $L_{\max}$ , mean cross-sectional area, ratio of resting force to total isometric force (RF/TF), contraction coupling under low loading conditions (R1), and load sensitivity of relaxation (Isot A/Isom A) among the five groups of papillary muscles (table 1). Control values of these mechanical parameters were similar to those observed in previous studies.<sup>14,17</sup>

Both ketamine  $10^{-4}$  and  $10^{-5}$  M lowered the duration of twitch (TPS, TPF), impaired the isotonic relaxation (maxVr), the load sensitivity of relaxation (Isot A/Isom A), and the contraction-relaxation coupling under low

TABLE 2. Mechanical Parameters of Papillary Muscles Exposed to Ketamine  $10^{-5}$  M or  $10^{-4}$  M at a  $[Ca^{++}]_0$  of 2.5 mM

|   | Group 1 (n = 8) |                      |                      | Group 2 (n = 8) |                      |                       |
|---|-----------------|----------------------|----------------------|-----------------|----------------------|-----------------------|
|   | Control         | Ketamine $10^{-4}$ M | % Control            | Control         | Ketamine $10^{-5}$ M | % Control             |
| <b>Contraction</b>                              |                 |                      |                      |                 |                      |                       |
| $V_{max}$ ( $L_{max}/s$ )                       | $3.66 \pm 0.26$ | $3.40 \pm 0.45$      | $93 \pm 11$          | $3.29 \pm 0.52$ | $3.98 \pm 0.93$      | $120 \pm 14^\dagger$  |
| max Vc ( $L_{max}/s$ )                          | $2.54 \pm 0.52$ | $2.27 \pm 0.43$      | $90 \pm 13$          | $2.17 \pm 0.42$ | $2.52 \pm 0.55$      | $115 \pm 9^\dagger$   |
| AF/s (mN)                                       | $64 \pm 24$     | $58 \pm 21$          | $93 \pm 26$          | $56 \pm 10$     | $58 \pm 12$          | $103 \pm 8$           |
| TPS (ms)  | $169 \pm 14$    | $157 \pm 17$         | $93 \pm 8^*$         | $179 \pm 22$    | $162 \pm 19$         | $91 \pm 3^\ddagger$   |
| TPT (ms)  | $156 \pm 16$    | $138 \pm 15$         | $89 \pm 5^\ddagger$  | $170 \pm 24$    | $149 \pm 19$         | $88 \pm 5^\ddagger$   |
| +dF/dtmax/s ( $mN \cdot s^{-1} \cdot mm^{-2}$ ) | $861 \pm 310$   | $768 \pm 325$        | $88 \pm 20$          | $629 \pm 145$   | $737 \pm 201$        | $116 \pm 14^*$        |
| <b>Relaxation</b>                               |                 |                      |                      |                 |                      |                       |
| max Vr ( $L_{max}/s$ )                          | $3.40 \pm 0.87$ | $2.21 \pm 0.40$      | $69 \pm 19^\dagger$  | $3.22 \pm 0.65$ | $2.55 \pm 0.52$      | $79 \pm 10^\ddagger$  |
| -dF/dtmax/s ( $mN \cdot s^{-1} \cdot mm^{-2}$ ) | $316 \pm 96$    | $295 \pm 132$        | $92 \pm 20$          | $247 \pm 56$    | $290 \pm 75$         | $117 \pm 18^*$        |
| <b>Contraction-relaxation coupling</b>          |                 |                      |                      |                 |                      |                       |
| R1 (low load)                                   | $0.71 \pm 0.09$ | $1.05 \pm 0.18$      | $151 \pm 29^\dagger$ | $0.68 \pm 0.10$ | $0.96 \pm 0.17$      | $141 \pm 13^\ddagger$ |
| R2 (heavy load)                                 | $2.81 \pm 0.97$ | $2.71 \pm 0.96$      | $98 \pm 14$          | $2.62 \pm 0.70$ | $2.61 \pm 0.69$      | $100 \pm 10$          |
| <b>Load sensitivity of relaxation</b>           |                 |                      |                      |                 |                      |                       |
| Isot A/Isom A                                   | $0.80 \pm 0.02$ | $0.86 \pm 0.02$      | $107 \pm 4^\dagger$  | $0.80 \pm 0.03$ | $0.85 \pm 0.02$      | $106 \pm 3^\ddagger$  |

Values are mean  $\pm$  SD. Student's *t* test for paired data.

\*  $P < 0.05$ .

$^\dagger P < 0.01$ .

$^\ddagger P < 0.001$ .

loading conditions (R1), while they did not modify contraction-relaxation coupling under heavy loading conditions (R2) (table 2, fig. 2). At a  $[Ca^{++}]_0$  of 2.5 mM, ketamine  $10^{-5}$  M had a positive inotropic effect as demonstrated by the increase in  $V_{max}$ , whereas this parameter remained unchanged with ketamine  $10^{-4}$  M; AF/s remained unchanged with ketamine  $10^{-5}$  and  $10^{-4}$  M (table 2).

Decreasing  $[Ca^{++}]_0$  from 2.5 to 0.5 mM in group 3 to 5 ( $n = 24$ ) induced a decrease in contractility as shown by the decrease in  $V_{max}$  ( $55\% \pm 11\%$ ) and AF/s ( $47\% \pm 13\%$ ). These results were consistent with previous reports.<sup>12,17</sup> Effects of lowering  $[Ca^{++}]_0$  on a typical papillary muscle are shown in figure 3. At low  $[Ca^{++}]_0$ , both ketamine  $10^{-4}$  and  $10^{-5}$  M had a positive inotropic effect as shown by a significant increase in  $V_{max}$  ( $147\% \pm 33\%$ ,  $P < 0.01$ , and  $135\% \pm 22\%$ ,  $P < 0.01$ , respectively) and in AF/s ( $152\% \pm 44\%$ ,  $P < 0.01$ , and  $120\% \pm 10\%$ ,  $P < 0.02$ , respectively). The positive inotropic effect of ke-

tamine  $10^{-4}$  M on a typical papillary muscle is shown in figure 3. Contraction-relaxation coupling under low loading conditions (R1) was not statistically modified by ketamine  $10^{-4}$  M ( $91\% \pm 10\%$ , NS) and  $10^{-5}$  M ( $107\% \pm 8\%$ , NS). Contraction-relaxation coupling under heavy loading conditions (R2) was not modified by ketamine  $10^{-4}$  M ( $100\% \pm 23\%$ , NS) and  $10^{-5}$  M ( $104\% \pm 14\%$ , NS).

Postrest recovery was studied in groups 3 and 4 at a  $[Ca^{++}]_0$  of 0.5 mM. As shown in figure 4, ketamine had a dual effect on rat papillary muscle. The positive inotropic effect of ketamine  $10^{-4}$  and  $10^{-5}$  M was obvious according to the increase in B0. Nevertheless, ketamine  $10^{-4}$  M decreased the potentiated contraction B1, whereas ketamine  $10^{-5}$  M maintained B1 unchanged compared with its control value (fig. 4).

The decay of mean AF/s during the postrest recovery period is shown in figure 5. This decay fitted well to an exponential curve ( $0.994 < R < 0.999$ ), and the control

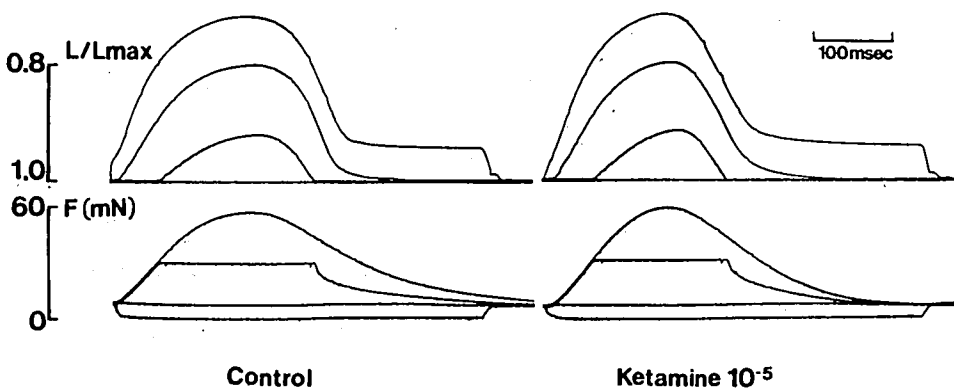
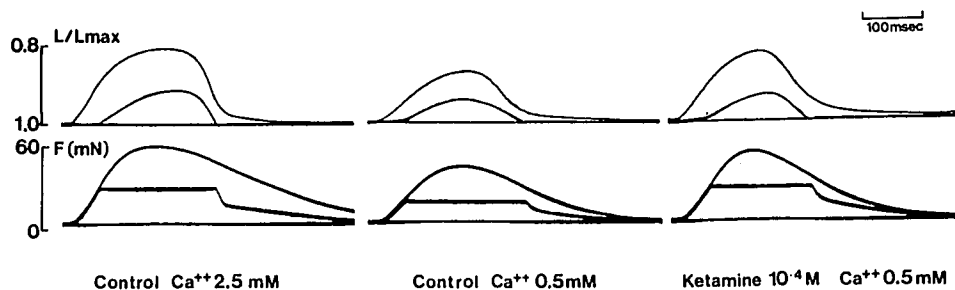


FIG. 2. Effects of ketamine  $10^{-5}$  M at a  $[Ca^{++}]_0$  of 2.5 mM on a typical papillary muscle. Upper graph: muscle shortening length ( $L/L_{max}$ ) was plotted versus time. Lower graph: force (F) was plotted versus time. This figure shows that ketamine reduced the duration of the twitch, increased isotonic shortening velocity and active isometric force, but impaired isotonic lengthening velocity and load sensitivity of the relaxation.

FIG. 3. Effects of ketamine  $10^{-4}$  M at a  $[Ca^{++}]_0$  of 0.5 mM on a typical papillary muscle. Upper graph: muscle shortening length ( $L/L_{max}$ ) was plotted versus time. Lower graph: force (F) was plotted versus time. To demonstrate the positive inotropic effect of ketamine,  $[Ca^{++}]_0$  was lowered from 2.5 to 0.5 mM, and then ketamine  $10^{-4}$  M was added. The zero-load clamp twitch was deleted to simplify the figure.



value of  $\tau$  did not differ between groups 3 and 4 ( $3.9 \pm 0.2$  vs.  $3.7 \pm 0.2$  beats, NS). Ketamine  $10^{-4}$  M increased  $\tau$  from  $3.9 \pm 0.2$  to  $5.4 \pm 0.3$  beats ( $P < 0.001$ ), whereas ketamine  $10^{-5}$  M did not significantly modify  $\tau$  from  $3.7 \pm 0.2$  to  $3.4 \pm 0.4$  (fig. 5).

In group 5 phentolamine  $10^{-6}$  M and propranolol  $10^{-6}$  M did not decrease the positive inotropic effect of ketamine  $10^{-4}$  M (fig. 6).

### Discussion

Ketamine is a rapid-acting iv anesthetic, which has been in clinical use for over 20 yr.<sup>5</sup> The cardiovascular stimulation induced by ketamine has prevented its widespread acceptance, although in many studies attempts have been made to counteract these circulatory side effects.<sup>5,22</sup> However, ketamine is recommended and widely used in critically ill patients, especially those with hypovolemia or cardiac tamponade.<sup>5</sup> In these patients the cardiovascular stimulation induced by ketamine is usually considered beneficial. Nevertheless, the cardiovascular action of ketamine results from various effects on different target organs: CNS, sympathetic nerve endings, vascular smooth muscle, and cardiac muscle.<sup>5</sup> Consequently, an "unexpected" decrease in blood pressure, heart rate, and cardiac output may be observed after ketamine injection in critically ill patients.<sup>4</sup> The direct effect of ketamine on the myocardium remains controversial because of conflicting results from experimental studies,<sup>8,9</sup> but the general consensus is that ketamine has a direct negative inotropic effect on intrinsic contractility.<sup>5</sup>

*In vivo* and in the absence of autonomic nervous control, ketamine induced a decrease in the maximum rise in the rate of left ventricular pressure ( $+dP/dt_{max}$ ) with beta adrenergic blockade and an increase in left ventricular end-diastolic pressure but no change in  $+dP/dt_{max}$  with combined beta adrenergic and cholinergic blockade.<sup>6</sup> Because these effects were transient and noted only 30 s after ketamine injection, the authors<sup>6</sup> have questioned their significance;  $+dP/dt_{max}$  is an isovolumetric systolic index, which varies with the inotropic status but also with afterload and heart rate,<sup>7</sup> and ketamine has been dem-

onstrated to modify both afterload and heart rate. A significant increase in cardiac output has been observed with ketamine and beta adrenergic blockade.<sup>6</sup> However, the precise effects of an anesthetic agent on myocardial contractility are difficult to assess *in vivo*.<sup>7</sup>

Our *in vitro* study clearly demonstrated that ketamine has a positive inotropic effect on rat myocardium. At a  $[Ca^{++}]_0$  of 2.5 mM, this positive inotropic effect was demonstrated only by an increase in  $V_{max}$  with ketamine  $10^{-5}$  M (table 2), which was consistent with previous results.<sup>8</sup> However, at such a  $[Ca^{++}]_0$ , contractility of rat myocardium is nearly at its maximum.<sup>10,12</sup> Therefore, it is not possible to quantify (or to compare) a positive inotropic effect at such high  $[Ca^{++}]_0$ . At a lower  $[Ca^{++}]_0$ , the positive inotropic effect was evident at both ketamine concentrations as shown by the increase in maximum unloaded shortening velocity ( $V_{max}$ ) and maximum isometric force (AF/s) (fig. 3).

Previous *in vitro* studies have produced conflicting evidence concerning the direct effect of ketamine on the

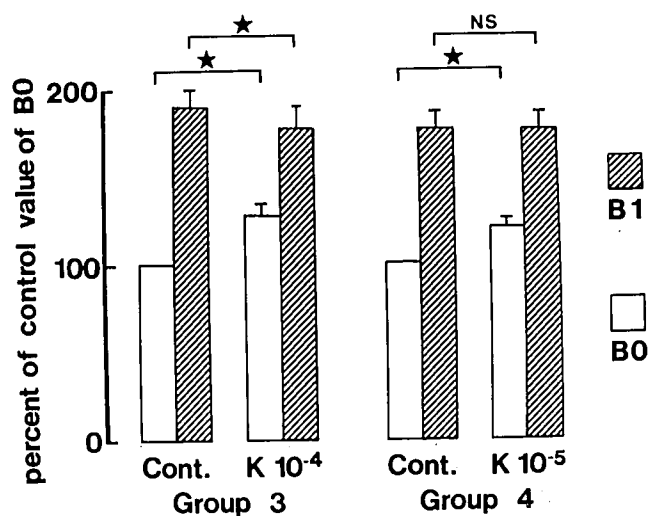


FIG. 4. Effects of ketamine  $10^{-4}$  M (group 3, n = 8) or  $10^{-5}$  M (group 4, n = 8) on postrest recovery. B0 = the beat before rest; B1 = the first beat after rest. Data are mean  $\pm$  SEM; paired Student's *t* test. \* $P < 0.05$ .

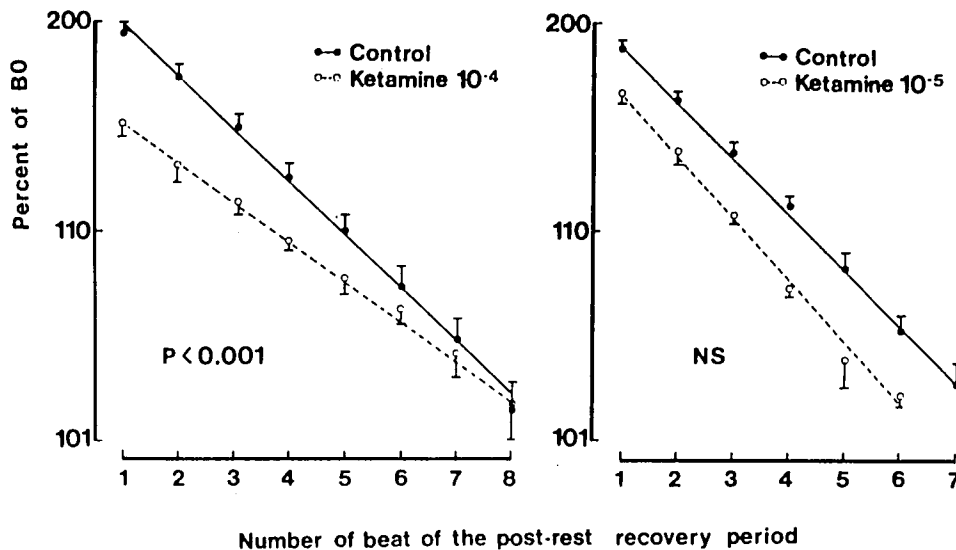


FIG. 5. Effect of ketamine  $10^{-4}$  (group 3,  $n = 8$ ) and  $10^{-5}$  (group 4,  $n = 8$ ) on the decay of active isometric force during the postrest recovery period. Data were expressed as mean percent of B0 (the beat before rest)  $\pm$  SEM and were plotted on a semilogarithmic scale.  $P$  value represents comparison of the slope of the regression curve using Student's  $t$  test.

myocardium. In the dog heart-lung preparation,<sup>1</sup> a decrease in cardiac output was only observed with high concentrations of ketamine ( $0.95 \times 10^{-3}$  M). In isolated rabbit heart, negative chronotropic and inotropic effects were reported,<sup>23</sup> but slowing heart rate in this preparation induces a decrease in isometric force (Bowditch phenomenon), and at the lowest concentration ( $5 \times 10^{-5}$  M), no significant decrease in contractile force was noted.<sup>23</sup> In rat left ventricular papillary muscle,<sup>8</sup> ketamine decreased isometric force, but high, suprathreshold, concentrations of ketamine were tested. At concentrations of  $10^{-5}$  and  $10^{-4}$  M, Goldberg *et al.*<sup>8</sup> have observed a nonsignif-

icant increase in  $V_{max}$  and isometric force, but the contractility of rat myocardium was nearly maximum before ketamine. Two other studies have clearly demonstrated that ketamine from  $10^{-5}$  to  $3 \times 10^{-4}$  M is actually a positive inotropic agent.<sup>9,24</sup> Our study confirms these previous results. However, all experimental studies have demonstrated that higher concentrations (beyond  $5 \times 10^{-4}$  M) have direct myocardial depressant action.<sup>1,8,23-25</sup>

Urthaler *et al.*<sup>24</sup> have reported that the positive inotropic effect of ketamine on isolated dog right ventricular trabeculae was abolished by propranolol or pretreatment with reserpine. Barrigon *et al.*<sup>9</sup> have recently demonstrated that the inotropic effect of ketamine on isolated rat atria was not modified by either propranolol or pretreatment with reserpine. Our study demonstrated that the positive inotropic effect of ketamine is not related to its catecholamine uptake inhibition for the following reasons: 1) it has been shown that catecholamines in rat papillary muscle are no longer present after a 1-h stabilization period *in vitro* because reserpine administration to the bathing solution did not induce any positive inotropic effect<sup>26</sup>; 2) the positive inotropic effect of ketamine developed slowly, attaining a maximum after 30–45 min, whereas the positive inotropic effect of catecholamines developed beat-to-beat, attaining a maximum at 15 min; 3) the positive inotropic effect of ketamine was not associated with a decrease in R2 (*i.e.*, a greater increase in isometric relaxation than in isometric contraction) as demonstrated with catecholamines<sup>27</sup>; and 4) ketamine remained a positive inotropic agent when both  $\alpha$  and  $\beta$  adrenergic receptors were blocked (fig. 6). These results also indicate that ketamine effects are not mediated by either  $\alpha$  or  $\beta$  receptors.

The precise mechanism of action for the positive inotropic effect of ketamine remains unknown, but some hy-

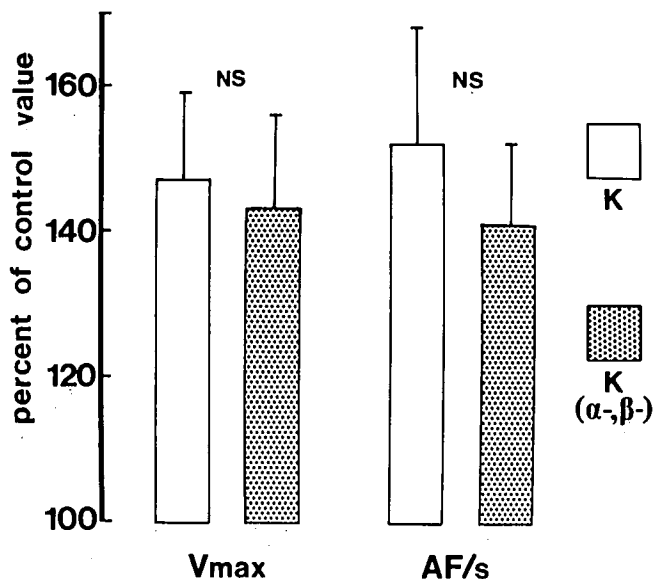


FIG. 6. Positive inotropic effect of ketamine  $10^{-4}$  M alone (K, group 3,  $n = 8$ ) and with phentolamine  $10^{-6}$  M and propranolol  $10^{-6}$  M (K  $[\alpha-, \beta-]$ , group 5,  $n = 8$ ).  $[Ca^{++}]_0$  was 0.5 mM. Data are mean  $\pm$  SEM; Student's  $t$  test.

potheses can be raised. A positive inotropic agent increases  $[Ca^{++}]_i$ , which comes from two main sources: sarcolemma and SR. An increase in the calcium-induced calcium release from the SR is unlikely because we demonstrated that ketamine decreased isotonic relaxation ( $\max V_r$ ), which suggests a decrease in calcium uptake by SR. Indeed, it has been demonstrated that an increase in calcium-induced calcium release is associated with an increase in calcium uptake.<sup>28</sup> Moreover, ketamine had no positive inotropic effect on the potentiated contraction B1, which is highly dependent on SR.<sup>13</sup> It is therefore unlikely that the positive inotropic effect of ketamine could be mediated by SR. Our study showed that ketamine did not enhance relaxation more than contraction (no change in R2 under heavy load) in association with its positive inotropic effect (increase in maximum active force) (fig. 7). Pharmacologic agents that increased cAMP in the rat heart (norepinephrine, isoproterenol, glucagon, and dibutyryl-cAMP) showed relaxing properties as demonstrated by a greater increase in isometric relaxation than in isometric contraction (*i.e.*, a decrease in R2 under heavy load)<sup>27</sup> (fig. 7). Increase in cAMP is responsible for the activation of a protein kinase that phosphorylates troponin I and therefore desensitizes actin filaments and induces a short duration of the isometric relaxation. Conversely, ouabain, which acts by increasing  $[Ca^{++}]_i$  *via* inhibition of the  $Na^+/K^+$  pump and consequently increases calcium influx *via* the  $Na^+/Ca^{++}$  exchange but does not modify myofilaments calcium sensitivity, does not modify R2 under heavy load<sup>27</sup> (fig. 7). These results show that the mechanical behavior of ketamine under heavy load is similar to that of ouabain, and suggest that the positive inotropic effect of ketamine could be related to an increase in calcium influx. This was previously suggested from the Barrigon *et al.* study,<sup>9</sup> which showed that ketamine increased calcium influx into isolated rat atria. Furthermore, ketamine increased B0 but not B1 (fig. 4). Bers<sup>13</sup> has demonstrated that B1 is more highly dependent on calcium stored in the SR than is B0, which is slightly more dependent on transsarcolemmic-derived calcium than is B1. Therefore, it is likely that the positive inotropic effect of ketamine is related to an increase in transsarcolemmal calcium influx. Nevertheless, the action of ketamine probably is more complex. We found that the action of ketamine on the intrinsic mechanical properties of the rat myocardium was not similar to that observed with ouabain because ketamine at a  $[Ca^{++}]_0$  of 0.5 mM did not impair contraction-relaxation coupling under low load (increase in R1), whereas ouabain did. Moreover, Adams *et al.*<sup>25</sup> have found that ketamine potentiated the inotropic effects of epinephrine, isoproterenol, and dibutyryl-cAMP, suggesting that ketamine might also modify the availability of cAMP. Lastly, ketamine might increase the calcium sensitivity of the myofilaments, but if the positive inotropic effect of

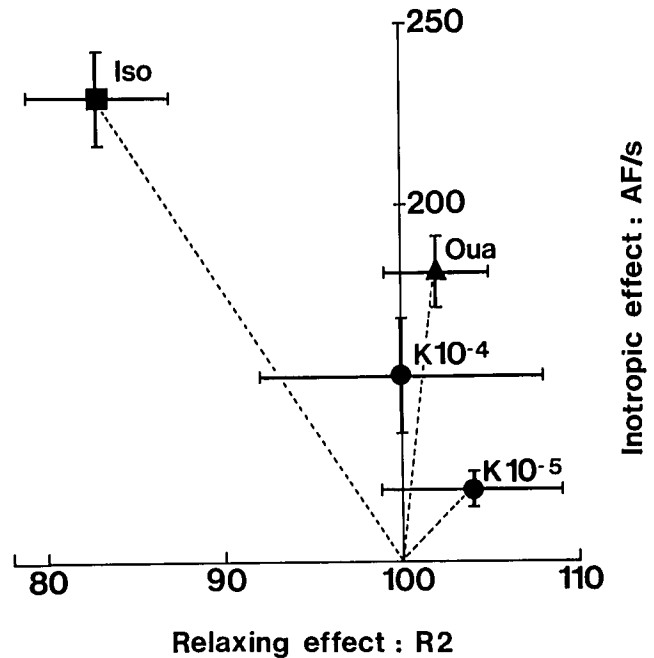


FIG. 7. Effects of ketamine (K)  $10^{-4}$  M (group 3,  $n = 8$ ) and  $10^{-5}$  M (group 3,  $n = 8$ ) on active isometric force (AF/s) and contraction-relaxation coupling under heavy loading conditions (R2).  $[Ca^{++}]_0$  was 0.5 mM. AF/s tested changes in inotropy whereas R2 tested relaxing effect. Data were expressed as mean percent of control values  $\pm$  SEM. In comparison with ketamine, isoproterenol  $5 \times 10^{-6}$  M (Iso,  $n = 8$ ) had a positive relaxing effect effect, whereas ouabain  $5 \times 10^{-8}$  M (Oua,  $n = 8$ ) had not.

ketamine was related to an increase in calcium sensitivity of myofilaments, a parallel increase in B0 and B1 would have been anticipated, which was not observed in our study (fig. 4).

Load sensitivity of relaxation reflects the capacity of mammalian cardiac muscle to regulate the time course of relaxation according to loading conditions. Load sensitivity of relaxation requires the presence of an effective calcium sequestering system, especially the SR.<sup>29</sup> Load-independent relaxation is typical in the frog<sup>29</sup> or newborn rat<sup>17</sup> myocardium in which the SR is poor and/or non-functional. Ketamine decreased the load sensitivity of relaxation (Isot A/Isom A). Such a decrease may result from an abbreviated isometric relaxation (decrease in myofilament sensitivity to calcium), a slowing of isotonic relaxation (decrease in calcium uptake by the SR), or both. Because we observed that 1) ketamine impaired isotonic relaxation ( $\max V_r$ ), and contraction-relaxation coupling under low load (R1), suggesting an impairment in the SR; and 2) ketamine did not decrease isometric relaxation speed ( $-dF/dt_{\max}$ ) or modify contraction-relaxation coupling under heavy load (R2) suggesting that ketamine did not decrease myofilaments sensitivity to calcium, we can assume that the decrease in load sensitivity was related to an impairment of the SR. However, ketamine did not



completely abolish the load dependence of relaxation as was observed with therapeutic concentration of volatile anesthetics.<sup>30</sup>

A relationship between inotropy and relaxation was demonstrated in rat myocardium.<sup>17</sup> Two hypotheses may explain why the impairment in relaxation observed with ketamine was not associated with a negative inotropic effect: 1) the action of ketamine on SR function was counterbalanced by other mechanisms underlying its positive inotropic effect; and 2) the action of ketamine on SR function was not sufficient to induce a significant negative inotropic effect. Our study provides evidence for both hypotheses: at a  $[Ca^{++}]_0$  of 2.5 mM, the major source of activator calcium is derived from the SR, and our study showed that a positive inotropic effect was found with ketamine  $10^{-5}$  M but not with ketamine  $10^{-4}$  M. This may suggest that the depressant effect of ketamine on SR function was more predominant at the highest concentration (but some reservation raises concerning the comparison of a positive inotropic effect at this high  $[Ca^{++}]_0$  as stated above). At a  $[Ca^{++}]_0$  of 0.5 mM, contraction is somewhat more dependent on transsarcolemmic calcium,<sup>21</sup> and ketamine  $10^{-5}$  M or  $10^{-4}$  M had a highly significant positive inotropic effect without impairing the contraction-relaxation coupling under low load (R1).

The characteristics of force postrest recovery in the rat ventricle have been extensively studied<sup>13,21</sup> and are shown in figure 5. The first beat of postrest recovery (B1) is more dependent on SR than subsequent beats and the beat before rest. This postrest potentiation is abolished by ryanodine, a specific inhibitor of SR calcium function, which locked the calcium release channels of the terminal cisternae of SR in the open state.<sup>31</sup> In our study a decrease in B1 was observed with ketamine  $10^{-4}$  M but not with ketamine  $10^{-5}$  M. These results suggest that only high concentrations of ketamine significantly impaired SR function and therefore diminished the potentiated state of contraction. Barrigon *et al.*<sup>9</sup> have reported that both concentrations of ketamine ( $10^{-5}$  and  $10^{-4}$  M) decreased postrest potentiation according to a decrease in the ratio B1/B0, but they did not account for the positive inotropic effect of ketamine, which increased B0 and consequently decreased the ratio B1/B0. As shown in figure 4, only ketamine  $10^{-4}$  M was able to decrease B1 slightly, reflecting a decrease in postrest contraction. Obviously, the ratio B1/B0 was decreased because of the positive inotropic effect of ketamine, which increased B0.

The decay of active force during the postrest recovery period has been shown to be exponential, and the rate constant  $\tau$  was thought to reflect SR function.<sup>21</sup> Our study showed that ketamine  $10^{-4}$  M increased  $\tau$ , whereas ketamine  $10^{-5}$  M did not, suggesting again that only high concentration of ketamine significantly impair SR function.

At a  $[Ca^{++}]_0$  of 2.5 mM, relaxation in unloaded muscle

was slowed by ketamine, whereas the relaxation of isometric twitch was unaffected. This observation might indicate also an impairment of the SR by ketamine. In isotonic conditions, the amplitude of sarcomere shortening is about twice that observed in isometric conditions,<sup>18</sup> and isotonic relaxation occurred earlier and more rapidly than isometric relaxation partly due to two mechanisms<sup>19</sup>: 1) the easier removal of calcium from troponin C due to the decrease of calcium sensitivity of myofilaments, itself linked to the sarcomere length; and 2) the rapid calcium uptake by the SR. Under low load the SR appears to play a major role in the regulation of relaxation, whereas under heavy load the sensitivity of myofilaments to calcium is higher and becomes therefore the limiting step that appears to play a major role in the regulation of relaxation. Nevertheless, there is another hypothesis that may explain why ketamine slowed isotonic and not isometric relaxation: ketamine might increase the sensitivity of troponin C to calcium in isotonic conditions (when few myosin heads are attached and troponin C sensitivity to calcium is low), which might result in a slowed isotonic relaxation. The experimental model is unable to definitely decide between these two hypothesis: an increase in troponin C sensitivity to calcium or a decrease in calcium uptake by the SR. Nevertheless, we have indicated above many arguments that favor the hypothesis of an SR effect of ketamine.

Therefore, ketamine has a dual action on the rat myocardium: it produces a positive inotropic effect and it impairs SR function. Nevertheless, the latter action is only significant at high concentrations ( $10^{-4}$  M) and might overcome the positive inotropic effect only at supratherapeutic concentrations.<sup>8,25</sup> Davies and McCans<sup>32</sup> have shown that high concentrations of ketamine (4 and  $8 \times 10^{-4}$  M) reversed the positive staircase of rabbit heart as observed with ryanodine, which inhibits SR function. These results<sup>32</sup> suggest that the negative inotropic effect of high concentrations of ketamine are due to an SR effect. During anesthesia the cardiostimulatory actions of ketamine consequently result from various mechanisms: 1) sympathomimetic effects mediated within the CNS<sup>2</sup>; 2) inhibition of intraneuronal and extraneuronal uptake of catecholamines<sup>3</sup>; 3) direct positive inotropic effect; and 4) myocardial potentiation of catecholamine-induced positive inotropic effects.<sup>8</sup> In critically ill patients, an unexpected decrease in blood pressure may result from the inability of sympathomimetic effects of ketamine to counterbalance its direct vasodilatory action<sup>33</sup> despite a direct positive inotropic effect or excessive plasma concentrations related to an inappropriate dose of ketamine. Experimental studies have shown that dosage of anesthetic agents had to be reduced 50–70% in hypovolemic animals.<sup>34</sup> Nevertheless, some remarks must be added to minimize the clinical implications of the present study. First, the positive inotropic effect of ketamine was not of

great importance compared with those of isoproterenol or ouabain (fig. 7). Second, this study was performed using rat myocardium, which differs from human myocardium: in rat myocardium a negative staircase (increase in stimulation frequency decreases force) is observed, and the SR is more developed than in any other species. Third, this study was an *in vitro* study and was conducted at 29° C; however, papillary muscles have to be studied at 29° C because stability of mechanical parameters is not sufficient at 37° C. Fourth, this study was conducted in normal animals. Because Chang *et al.*<sup>35</sup> have found that ketamine was a negative inotropic agent on human isolated atrial tissue obtained from patients requiring open heart surgery, understanding of the effects of ketamine in patients with cardiac disease requires further investigation.

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