

## Effects of Ketamine on the Cardiac Papillary Muscle of Normal Hamsters and Those with Cardiomyopathy

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The effect of ketamine ( $10^{-5}$  and  $10^{-4}$  M) on the intrinsic contractility of left ventricular papillary muscle from normal hamsters and those with cardiomyopathy (BIO 82.62, 6-month old) was investigated. At these concentrations, ketamine induced a positive inotropic effect on normal papillary muscle, as shown by an increase in maximum unloaded shortening velocity ( $+19 \pm 4$  and  $+34 \pm 5\%$ ,  $P < 0.05$ ), active isometric force ( $+32 \pm 8$  and  $+57 \pm 11\%$ ,  $P < 0.05$ ), and peak power output ( $+40 \pm 8$  and  $+80 \pm 16\%$ ,  $P < 0.05$ ), and induced a slight decrease in sarcoplasmic reticulum function. Ketamine had no effect on the curvature of the total force-velocity curve, suggesting that it does not modify myothermal economy. Contractility of papillary muscle from hamsters with cardiomyopathy was less than that of controls, as shown by the decrease in isometric active force ( $-41\%$ ,  $P < 0.02$ ), peak power output ( $-33\%$ ,  $P < 0.05$ ), and sarcoplasmic reticulum function. The positive inotropic effect of ketamine on papillary muscle from hamsters with cardiomyopathy was less marked than in controls and almost suppressed in some cases: only the maximum unloaded shortening velocity was significantly increased with  $10^{-5}$  M ketamine ( $+7 \pm 6\%$ ,  $P < 0.05$ ), whereas no significant changes were observed in active isometric force ( $+14 \pm 8$  and  $+13 \pm 11\%$ ; nonsignificant [NS]) and peak power output ( $+9 \pm 5$  and  $+13 \pm 8\%$ ; NS) with ketamine ( $10^{-5}$  and  $10^{-4}$  M, respectively). The effects of ketamine on contraction-relaxation coupling under low and heavy loads were similar to those observed with normal muscle. The direct mechanical effects of ketamine on cardiac muscle therefore depend on the pathophysiologic state; ketamine did not induce a significant inotropic effect on cardiomyopathic muscles. (Key words: Anesthetics, intravenous: ketamine. Heart: cardiomyopathy. Heart, papillary muscle: contractility; relaxation.)

KETAMINE, which has been shown to produce marked cardiovascular stimulation, is recommended in critically ill patients for induction of anesthesia.<sup>1</sup> The cardiovascular

action of ketamine results from various effects on different target organs: 1) sympathomimetic effects mediated within central nervous system structures<sup>2</sup>; 2) inhibition of neuronal uptake of catecholamines by sympathetic nerve endings<sup>3</sup>; 3) direct vasodilation of vascular smooth muscle<sup>4</sup>; and 4) inotropic effect on myocardial muscle. The direct effects of ketamine on cardiac muscle, *i.e.*, positive or negative inotropic effects, may be important during induction of anesthesia in critically ill patients. We have recently demonstrated that ketamine is a positive inotropic agent on isolated rat cardiac papillary muscle.<sup>5</sup> These results confirmed previous data of Barrigon *et al.*<sup>6</sup> However, our study in fact showed that ketamine has a dual action on the myocardium: 1) a positive inotropic effect probably related to an increased calcium ( $\text{Ca}^{++}$ ) influx; 2) an impairment of sarcoplasmic reticulum (SR) function. We showed that this impairment of SR function is only significant at high ketamine concentrations and only overcomes the positive inotropic effect at supratherapeutic concentrations.<sup>5</sup> Because our previous experimental study<sup>5</sup> was conducted on normal myocardium, we sought to determine if ketamine still induces a positive inotropic effect on diseased myocardium, as the combination of the two opposing effects of ketamine (increase in  $\text{Ca}^{++}$  influx and decrease in SR function) may differ in the diseased myocardium in which  $\text{Ca}^{++}$  handling and/or SR function are already modified.<sup>7</sup>

The selective breeding of strains of Syrian hamsters with hereditary cardiomyopathy has offered a unique opportunity for investigating myocardial function.<sup>8</sup> Among experimental models of cardiac failure, genetically determined cardiomyopathies have some advantages: 1) contractility, cellular biochemistry, and physiology have been extensively studied in these experimental models<sup>9</sup>; 2) the time course of cardiac failure is well known, so that animal may be studied at a given stage of the disease; 3) impairment in contractility is primarily due to cardiac muscle cell disease and is not secondary to acute pressure or volume overload and/or to drug-induced cardiac toxicity, and therefore may be more relevant to clinical cardiomyopathies.<sup>10</sup>

We therefore conducted an *in vitro* study of the effects of ketamine on the intrinsic contractility of cardiac papillary muscles from normal hamsters and hamsters with cardiomyopathy.

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## Materials and Methods

### ANIMALS

Five normal Syrian hamsters and five Syrian hamsters with cardiomyopathy (strain BIO 82.62) were used in this study (Charles River, France). The BIO 82.62 strain has been obtained by crossing the well-known cardiomyopathic strain BIO 14.6 with a healthy strain BIO RB. In strain BIO 82.62 as in strain BIO 14.6, all animals of both sexes develop cardiomyopathy from the age of 6 weeks.<sup>11</sup> However, unlike in strain BIO 14.6, no clear cardiac hypertrophy occurs in strain BIO 82.62.<sup>11</sup>

Care of the animals conformed to the recommendations of the Helsinki Declaration, and the study was authorized by our institution (INSERM). All animals were aged 6 months. Body weight (BW), heart weight (HW), and left ventricular weight (LVW) were determined at the moment of killing. The per cent of cardiac and left ventricular hypertrophy in hamsters with cardiomyopathy was calculated from the HW/BW and LVW/BW ratios normalized per the mean value of the same ratios determined in control animals. Table 1 summarizes the main characteristics of normal hamsters and those with cardiomyopathy.

### EXPERIMENTAL PROTOCOL

Twenty left ventricular papillary muscles (two from each hamster) were studied. 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<sub>4</sub>·7H<sub>2</sub>O, 1.1 KH<sub>2</sub>PO<sub>4</sub>, 25 NaHCO<sub>3</sub>, 2.5 CaCl<sub>2</sub>·6H<sub>2</sub>O, and 4.5 glucose. Preparations were field stimulated at 3/min by two platinum electrodes with rectangular wave pulses of 5-ms duration just above threshold. This stimulation frequency corresponds to the apex of the force–frequency relationship. The bathing solution was bubbled with 95% O<sub>2</sub>–5% CO<sub>2</sub>, giving a pH of 7.40, and the temperature was maintained at 29° C. After a 1-h stabilization period at L<sub>max</sub> (i.e., the initial muscle length at the apex of the length–active isometric tension curve), papillary muscles recovered their optimal mechanical performance, which were

stable for many hours. Table 2 summarizes the muscle characteristics during control conditions at L<sub>max</sub>.

Control values of each mechanical parameter were recorded, and ketamine hydrochloride (Ketalar®) then was added to the bathing solution. Two concentrations of ketamine were tested in a cumulative manner: 10<sup>-5</sup> M, corresponding to serum concentrations of ketamine obtained during maintenance of anesthesia,<sup>12</sup> and 10<sup>-4</sup> M, corresponding to peak serum concentrations obtained during induction of anesthesia.<sup>12</sup> These two concentrations are those previously tested in normal rat myocardium.<sup>5</sup> At the end of the study, the cross-sectional area(s) was calculated from the length and weight of papillary muscle, assuming a density of 1.

### ELECTROMAGNETIC LEVER SYSTEM AND RECORDING

The electromagnetic lever system has been previously described.<sup>13</sup> Briefly, the load applied to the muscle was determined by a servo-controlled current through the coil of the electromagnet. Muscular shortening induced a displacement of the lever, which modulated the light intensity of a photoelectric transducer. All analyses were made from digital records obtained with a Hewlett Packard 1000 computer as previously described.<sup>5</sup>

### MECHANICAL PARAMETERS

Conventional mechanical parameters at L<sub>max</sub> were calculated from three twitches. The first twitch was isotonic and was loaded with the preload only at L<sub>max</sub>. The second twitch was abruptly clamped to zero-load just after the electrical stimulus (<3 msec); the maximum unloaded shortening velocity (V<sub>max</sub>) was determined from this twitch. The third twitch was fully isometric at L<sub>max</sub>. The mechanical parameters characterizing the contraction and relaxation phases, and coupling between contraction and relaxation are defined as follows:

#### Contraction Phase

Parameters involved in the contraction phase were: maximum unloaded shortening velocity (V<sub>max</sub>) by means of the zero-load clamp technique<sup>14</sup>; maximum shortening velocity (maxVc) of the twitch with preload only; maxi-

TABLE 1. Characteristics of Normal Hamsters and of Those with Cardiomyopathy

Hamsters	BW (g)	HW (mg)	LVW (mg)	HW/BW (10 <sup>-3</sup> )	LVW/BW (10 <sup>-3</sup> )	% Hypertrophy	
						Heart	LV
Normal (n = 5)	131 ± 3	490 ± 13	364 ± 9	3.74 ± 0.05	2.78 ± 0.05	100	100
Cardiomyopathic (n = 5)	108 ± 2*	411 ± 11*	339 ± 10	3.81 ± 0.07	3.14 ± 0.11	102 ± 2	113 ± 4

Values are mean ± SE; \*P < 0.05.

TABLE 2. Characteristics of Papillary Muscles of Normal Hamsters and Those with Cardiomyopathy

Hamsters	$L_{\max}$ (mm)	$s$ ( $\text{mm}^2$ )	RF/TF
Normal (n = 10)	$4.3 \pm 0.3$ (3.0–6.3)	$0.70 \pm 0.03$ (0.56–0.86)	$0.13 \pm 0.01$ (0.09–0.17)
Cardiomyopathic (n = 10)	$3.2 \pm 0.3^*$ (2.0–4.2)	$0.95 \pm 0.05^*$ (0.70–1.06)	$0.19 \pm 0.04$ (0.09–0.26)

Values are mean  $\pm$  SE (range);  $L_{\max}$  = initial length;  $s$  = cross-sectional area; RF/TF = ratio of resting force to total force; \* $P < 0.05$ .

imum isometric active force normalized per cross-sectional area (AF/s); peak of the positive force derivative per  $\text{mm}^2$  ( $+dF \cdot dt^{-1}/s$ ); 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 high load, respectively.

#### Relaxation Phase

The parameters involved in the relaxation phase were: maximum lengthening velocity of the twitch with preload only ( $\max V_r$ ), and the peak of the negative force derivative at  $L_{\max}$  normalized per cross-sectional area ( $-dF \cdot dt^{-1}/s$ ). These two parameters tested the lusitropic state of papillary muscle under low and high load, respectively. However, because the relaxation phase depends on the contraction phase, variations of contraction and relaxation must be simultaneously considered to quantify the drug-induced changes in relaxation. Therefore, indexes that test the contraction–relaxation coupling have been developed.<sup>15</sup>

#### Contraction–Relaxation Coupling

Coefficient  $R_1 = \max V_c / \max V_r$  tests the coupling between contraction and relaxation under low load. Under isotonic conditions the amplitude of sarcomere shortening is twice that observed under isometric conditions.<sup>16</sup> Because of the lower affinity of cardiac muscle troponin for  $\text{Ca}^{++}$  when it is rapidly shortening under low load, relaxation proceeds more rapidly than contraction, apparently because of rapid SR uptake of  $\text{Ca}^{++}$ . Thus,  $R_1$  (contraction–relaxation coupling under low load) is significantly less than 1 and tests SR function. Coefficient  $R_2 = (+dF \cdot dt^{-1}) / (-dF \cdot dt^{-1})$ , tests the coupling between contraction and relaxation under high load. When muscle is contracting isometrically, sarcomeres shorten less.<sup>16</sup> Because of a higher affinity of cardiac muscle troponin for  $\text{Ca}^{++}$ , relaxation is primarily determined by unbinding of  $\text{Ca}^{++}$ , not by SR. Thus,  $R_2$  (contraction–relaxation

coupling under heavy load) is greater than 1 and tests myofilament calcium sensitivity.

#### ENERGETIC PARAMETERS

The force–velocity curve was derived from the peak shortening velocity ( $V$ ) of 7–9 afterloaded twitches plotted against the total force normalized per cross-sectional area (TF/s), and from that of the zero-load clamp twitch as previously described.<sup>17</sup> The following energetic parameters were derived from Hill's equation<sup>18</sup> of the hyperbola (TF/s– $V$  relationship): the peak power output ( $\dot{E}_{\max}$ ), and curvature of the hyperbola ( $G$ ). The curvature of the force–velocity curve has been shown to be linked to the myothermal economy and cross-bridge kinetics<sup>17,19</sup>; the more curved the Hill's hyperbola (*i.e.*, the higher the value of  $G$ ), the higher the muscle efficiency. During cardiac hypertrophy, impaired myocardial performance is associated with an increase in  $G$  and a higher myothermal economy.<sup>17,19</sup>

#### STATISTICAL ANALYSIS

Data were expressed as mean  $\pm$  standard error of the mean (SE). Control values in normal hamsters and those with cardiomyopathy were compared by means of the Student's  $t$  test. The effects of ketamine in normal hamsters and those with cardiomyopathy were compared by repeated-measures two-way analysis of variance and the Student's  $t$  test with Bonferroni's correction. To determine the parameters of the Hill's equation, multiple linear regression was performed using the least squares method, as previously described.<sup>20</sup> All  $P$  values were two-tailed and a  $P$  value less than 0.05 was necessary to reject the null hypothesis.

#### Results

Body weight (BW) and heart weight (HW) of hamsters with cardiomyopathy were slightly lower than those of normal hamsters, although no cardiac hypertrophy was observed, as shown by the lack of increase in the HW/BW ratio (table 1). However, papillary muscle cross-sectional area was slightly greater in hamsters with cardiomyopathy than in normal hamsters (table 2).

The intrinsic mechanical performance of papillary muscles from hamsters with cardiomyopathy was significantly lower during the isometric twitch (AF/s,  $+dF \cdot dt^{-1}/s$ ), but not during isotonic twitches ( $V_{\max}$ ,  $\max V_c$ ) (table 3). This was partly related to the increase in papillary muscle cross-sectional area, as the difference in non-normalized active force (AF) between papillary muscles from normal hamsters and hamsters with cardiomyopathy ( $32 \pm 3$  vs.  $26 \pm 5$  mN) was not statistically significant. The peak power output ( $\dot{E}_{\max}$ ) was lower for

TABLE 3. Mechanical Parameters of Papillary Muscle of Normal Hamsters and of Those with Cardiomyopathy

Parameter	Normal (n = 10)	Cardiomyopathy (n = 10)	P
<b>Contraction</b>			
$V_{max}$ ( $L_{max} \cdot s^{-1}$ )	3.05 ± 0.09	2.83 ± 0.22	NS
maxVc ( $L_{max} \cdot s^{-1}$ )	1.97 ± 0.09	1.87 ± 0.21	NS
AF/s ( $mN \cdot mm^{-2}$ )	46 ± 5	27 ± 5	0.02
+dF · dt <sup>-1</sup> /s ( $mN \cdot s^{-1} \cdot mm^{-2}$ )	546 ± 49	366 ± 70	0.05
TPS (ms)	164 ± 3	142 ± 3	0.001
TPF (ms)	150 ± 2	127 ± 3	0.001
<b>Energetics</b>			
$\dot{E}_{max}$ ( $mN \cdot L_{max} \cdot s^{-1} \cdot mm^{-2}$ )	26 ± 2	17 ± 2	0.05
G	2.49 ± 0.15	2.33 ± 0.31	NS
<b>Relaxation</b>			
maxVr ( $L_{max} \cdot s^{-1}$ )	3.02 ± 0.20	2.35 ± 0.31	NS
-dF · dt <sup>-1</sup> /s ( $mN \cdot s^{-1} \cdot mm^{-2}$ )	351 ± 49	238 ± 40	NS
<b>Contraction-relaxation coupling</b>			
R1 (low load)	0.66 ± 0.02	0.83 ± 0.03	0.001
R2 (high load)	1.60 ± 0.09	1.49 ± 0.06	0.001

Values are mean ± SE; NS = nonsignificant.

cardiomyopathic muscles, whereas the curvature of the force-velocity relationship (G) remained unchanged. The two parameters that test contraction-relaxation coupling under low (R1) and high (R2) load were different: for cardiomyopathic muscles, R1 was higher, whereas R2 was lower than for normal muscles (table 3). A reduction in the time-to-peak shortening (TPS) and time-to-peak force (TPF) was noted with cardiomyopathic muscle in comparison with muscle from controls (table 3).

Ketamine ( $10^{-5}$  and  $10^{-4}$  M) induced a marked positive inotropic effect on normal muscle as shown by the increase in the maximum unloaded shortening velocity ( $V_{max}$ ), and the active isometric force (AF/s) (fig. 1). In contrast, in cardiomyopathic muscles, these two parameters remained unchanged, except for  $V_{max}$  with  $10^{-5}$  M ketamine (fig. 1). At each ketamine concentration, there were highly significant differences in the amplitude of the inotropic effect between the papillary muscles from normal hamsters and those with cardiomyopathy. The peak power output ( $\dot{E}_{max}$ ) of normal muscle markedly increased with  $10^{-5}$  and  $10^{-4}$  M ketamine, whereas no significant changes were observed with cardiomyopathic muscle (table 4). Ketamine had no significant effect on the curvature of Hill's hyperbola (G) in either groups. As shown in figure 2, the force-velocity curve was shifted to the right with normal muscle, but not with cardiomyopathic muscle.

The effects of ketamine on the relaxation phase (lusitropic effects) were markedly different between the two groups. A marked positive lusitropic effect was observed on normal muscle, both under low load (increase in maxVr) (fig. 3) and under high load (increase in -dF · dt<sup>-1</sup>) (fig. 4). In contrast, no significant lusitropic effects were observed with ketamine under either low or high load with cardiomyopathic muscle (figs. 3 and 4).

However, because the effects of ketamine on the contraction phase (inotropic effect) were different in the two groups, it was essential to determine contraction-relaxation coupling parameters to compare the effects of ketamine on the relaxation phase. Ketamine impaired contraction-relaxation coupling under low load (increase in R1) in both groups, with no significant differences between groups (fig. 3). Under high load, ketamine increased R2 ( $P < 0.01$ ), but this increase only reached statistical significance with  $10^{-5}$  M ketamine for normal muscle, and  $10^{-4}$  M ketamine for cardiomyopathic muscle,

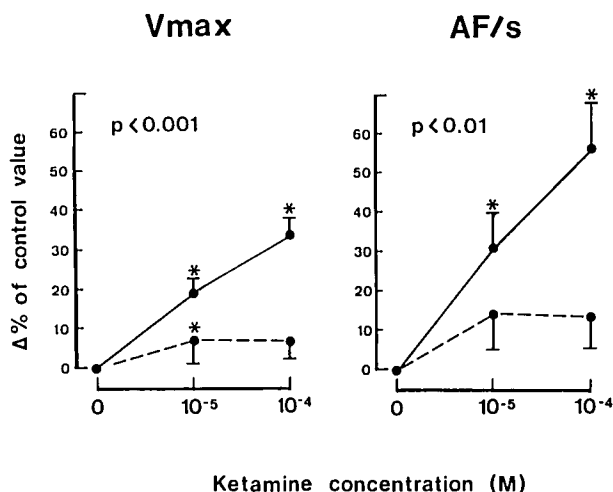


FIG. 1. Comparison of the inotropic effects of ketamine on the maximum unloaded shortening velocity ( $V_{max}$ ) and the active force normalized per cross-sectional area (AF/s) of papillary muscles of normal hamsters (solid line) and those with cardiomyopathy (dashed line). Data are mean ± SE. The P value concerns the between-group comparisons. \* $P < 0.05$  versus control values.

TABLE 4. Effects of Ketamine on the Energetic Parameters of Papillary Muscles from Normal Hamsters and from Those with Cardiomyopathy

Parameter	10 <sup>-5</sup> M Ketamine		10 <sup>-4</sup> M Ketamine		P
	Normal	Cardiomyopathy	Normal	Cardiomyopathy	
$\dot{E}_{max}$	+40*	+9	+80*	+13	0.001
	±8	±5	±16	±8	
G	+13	-1	+23	-4	NS
	±6	±10	±12	±12	

Values are per cent change from control values ± SE. P value concerns comparison between papillary muscles of normal hamsters and those with cardiomyopathy. \*P < 0.05 as compared to control values. NS = nonsignificant.

and was not of great amplitude. However, no differences were noted between the two groups (fig. 4).

With 10<sup>-5</sup> and 10<sup>-4</sup> M ketamine, respectively, no changes were observed in the time-to-peak shortening (TPS) of normal (-1.1 ± 1.4%; 0.2 ± 1.5%) or of cardiomyopathic muscle (-1.7 ± 1.2%; -0.4 ± 1.8%). Similar results were obtained for the time-to-peak force (TPF) of normal (-3.1 ± 2.4%; -1.1 ± 2.0%) and cardiomyopathic muscle (0.3 ± 2.8%; 7.2 ± 4.8%).

Discussion

EFFECTS OF KETAMINE ON PAPILLARY MUSCLE FROM NORMAL HAMSTERS

Ketamine (10<sup>-5</sup> and 10<sup>-4</sup> M) induced a positive inotropic effect as shown by the increase in maximum unloaded shortening velocity (V<sub>max</sub>: +19% and +34%, respectively) and active isometric force (AF/s: +32% and +57%, respectively) (fig. 1). This positive inotropic effect on hamster myocardium is consistent with our findings in rat myocardium at 0.5 mM Ca<sup>++</sup> with 10<sup>-5</sup> (V<sub>max</sub>: +35%; AF/s: +20%) and 10<sup>-4</sup> M ketamine (V<sub>max</sub>: +47%;

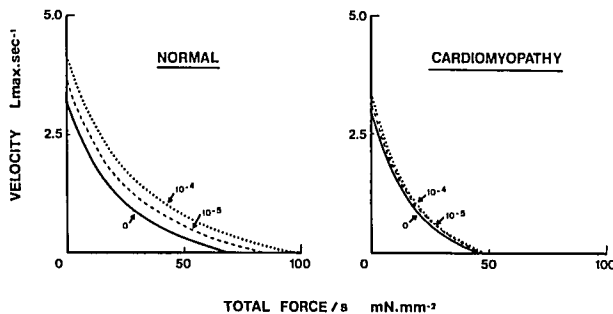


FIG. 2. Effects of different ketamine concentrations (0, 10<sup>-5</sup>, or 10<sup>-4</sup> M) on the total force-velocity relationship of papillary muscles of normal hamsters and those with cardiomyopathy.

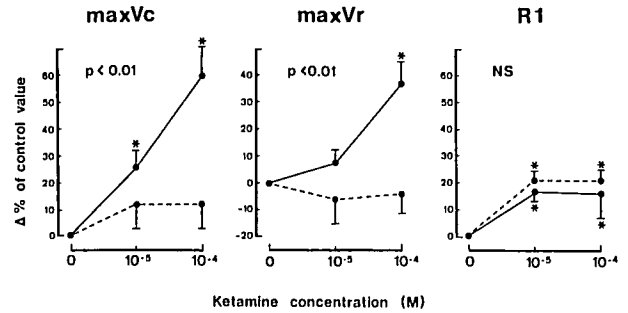


FIG. 3. Comparison of the effects of ketamine on the maximum shortening velocity (maxVc), maximum lengthening velocity (maxVr), and contraction-relaxation coupling under low load (R1 = maxVc/maxVr) of papillary muscles of normal hamsters (solid line) and those with cardiomyopathy (dashed line). Data are mean ± SE. The P value concerns the between-group comparison. \*P < 0.05 versus control values. NS = nonsignificant.

AF/s: +52%).<sup>5</sup> Several *in vitro* studies gave conflicting evidence about the direct effect of ketamine on the myocardium.<sup>6,21,22</sup> These discrepancies probably were due to the concentration range tested and the dual effect of ketamine on cardiac muscle, as ketamine has a positive inotropic effect by increasing Ca<sup>++</sup> influx and, conversely, a possible negative inotropic effect by inhibiting SR function.<sup>5</sup> However, the impairment in SR function is only significant at high concentrations (10<sup>-4</sup> M) and is thought to overcome the positive inotropic effect only at supratherapeutic concentrations (above 10<sup>-4</sup> M). Hence, a positive inotropic effect was observed when therapeutic concentrations were tested,<sup>6</sup> whereas a negative inotropic effect was noted with supratherapeutic concentrations.<sup>21,22</sup> Our results with normal hamster papillary muscle confirm previous results in normal rat demonstrating that keta-

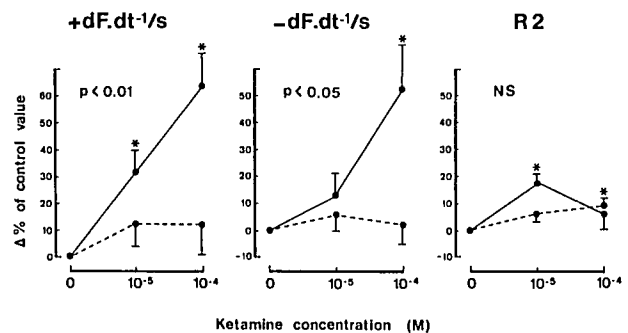


FIG. 4. Comparison of the effects of ketamine on the maximum rise (+dF · dt<sup>-1</sup>/s) and fall (-dF · dt<sup>-1</sup>/s) of the isometric force, and contraction-relaxation coupling under high load (R2 = +dF · dt<sup>-1</sup>/-dF · dt<sup>-1</sup>) of papillary muscles of normal hamsters (solid line) and those with cardiomyopathy (dashed line). Data are mean ± SE. The P value concerns the between-group comparison. \*P < 0.05 versus control values. NS = nonsignificant.

mine actually induces a positive inotropic effect at therapeutic concentrations.<sup>5</sup> Nevertheless, in rat and hamster myocardium, a negative staircase (increase in stimulation frequency decreases force) is observed, contractility is high, and the myosin isoforms are predominantly of the fast V1 type. In rabbit myocardium, a positive staircase is observed and the myosin isoforms are predominantly of the V3 type (as in human myocardium), and ketamine has been shown to induce a negative inotropic effect in rabbit papillary muscle.<sup>23</sup> Thus, inotropic effect of ketamine on human myocardium remains presently speculative.

Ketamine increased the maximum lengthening velocity ( $\max V_r$ ) to a lesser degree than the maximum shortening velocity ( $\max V_c$ ), resulting in an impairment in contraction-relaxation coupling under low load (increase in R1) (fig. 3). Under low load, the SR appears to play a major role in the regulation of isotonic relaxation. The increase in R1 observed with ketamine therefore suggests a decrease in SR function as previously observed in rat myocardium.<sup>5</sup> The increase in R1 with  $10^{-5}$  and  $10^{-5}$  M ketamine was lower in hamsters (+17% and +16%, respectively) than in rats at 2.5 mM  $\text{Ca}^{++}$  (+51% and 41%, respectively).<sup>5</sup> This result was not surprising, as SR function in rat myocardium at 2.5 mM  $\text{Ca}^{++}$  is very high.<sup>24</sup>

The effects of ketamine on hamster myocardium differed from those observed on rat myocardium in two ways: 1) the contraction-relaxation coupling under high load (R2) (fig. 4) and 2) the time-to-peak shortening (TPS) and time-to-peak force (TPF). Under isometric conditions, the myofilaments  $\text{Ca}^{++}$  sensitivity is higher and plays a major role in the regulation of the time course of isometric relaxation. The increase in R2 observed with ketamine therefore suggests that ketamine increases the  $\text{Ca}^{++}$  sensitivity of myofilaments, which may partly participate in the positive inotropic effect. However, an increase in calcium influx *per se* has been shown to increase coefficient R2.<sup>15</sup> Therefore, our results do not allow us to conclude about a possible effect of ketamine on myofilament  $\text{Ca}^{++}$  sensitivity in normal hamster myocardium. The differences between the amplitude of the effect of ketamine in hamster and rat myocardium may be related to species differences. Indeed, the mean control value of R2 was different in hamster ( $1.60 \pm 0.29$ ) and rat myocardium ( $2.72 \pm 0.82$ ),<sup>5</sup> suggesting species differences in the mechanical function of contractile proteins under high load. Moreover, the increase in R2 was not of great amplitude and was significant only at  $10^{-5}$  M ketamine. In the present study, ketamine did not modify TPS and TPF in normal hamsters, whereas these two parameters decreased in rat.<sup>5</sup> These differences may indicate different effects of ketamine on excitation-contraction coupling in hamster compared with those in rat. However, because no electro-

physiologic data were obtained in the present study, the reason for these differences remains unknown.

Our study is the first to provide some information about energetics of normal papillary muscles exposed to ketamine. A shift in the force-velocity curve to the right was observed (fig. 2), indicating a positive inotropic effect. The peak power output ( $\dot{E}_{\max}$ ) increased (table 4) as a result of an increase in both maximum unloaded shortening velocity and total isometric force. However, a non-significant increase in the curvature (G) of the hyperbola was observed with ketamine. G has been shown to be linked to myothermal economy and cross-bridges kinetics<sup>17,19</sup>: the higher value of G, the higher the muscle efficiency. Consequently, our results suggest that ketamine did not significantly modify cross-bridges kinetics or muscle efficiency, despite a marked positive inotropic effect. The fact that ketamine has no significant effect on the muscle efficiency may be considered to be beneficial from a myothermal point of view, in particular, in comparison with other positive inotropic agents such as epinephrine, which recently was shown to increase cross-bridges kinetics<sup>25</sup> and therefore decrease muscle efficiency.

#### MYOCARDIAL CONTRACTILITY OF PAPILLARY MUSCLE FROM HAMSTERS WITH CARDIOMYOPATHY

Cardiomyopathy in Syrian hamsters is characterized by the progressive occurrence of focal myocardial degeneration, fibrosis, and calcification during the life of the animal.<sup>7,9</sup> At 30-40 days, histologic lesions become apparent and myocardial performance decreases. Further cardiac changes include hypertrophy and/or dilation depending on the strain, then congestive heart failure and death. In our study, the myocardial performance of papillary muscle from hamsters with cardiomyopathy was impaired as reflected by the marked decrease in the peak power output ( $\dot{E}_{\max}$ ). The decreased myocardial performance may be explained by the previously reported decrease in the activity of G regulatory proteins,<sup>26</sup> decreased sarcolemmal  $\text{Ca}^{++}$  ATPase and  $\text{Na}^+, \text{K}^+$  ATPase activities,<sup>27</sup> increased density of voltage-sensitive  $\text{Ca}^{++}$  channels,<sup>28</sup> alterations in the creatine kinase system,<sup>29</sup> and in SR function,<sup>30</sup> modification of the sensitivity of myofilaments to  $\text{Ca}^{++}$ ,<sup>29</sup> and an isomyosin shift from the V1 toward the V3 type (which has the lowest ATPase activity).<sup>31</sup> A recent study supports the hypothesis of microvascular spasm leading to focal injury.<sup>32</sup> This is considered to be an extremely valuable experimental model for studying cardiomyopathy that results in progressive cardiac failure over a prolonged period, as in humans.

In our study, a nonsignificant decrease in  $V_{\max}$  was observed in hamsters with cardiomyopathy, suggesting that the isomyosin shift toward the V3 type was either absent

or moderate, as  $V_{\max}$  correlates with the myosin ATPase activity.<sup>33</sup> The lack of significant modification of the curvature of the Hill's hyperbola (G) also suggests that no major isomyosin shift occurred in hamsters with cardiomyopathy, as such a shift is responsible for a higher myothermal economy and consequently for an increase in G. Coefficient R2 of cardiomyopathic muscles was lower than that of the controls, suggesting that myofilament  $\text{Ca}^{++}$  sensitivity was lower in hamsters with cardiomyopathy. However, previous studies gave conflicting results about changes in the  $\text{Ca}^{++}$  sensitivity of myofilaments in the hamsters with cardiomyopathy.<sup>29,34</sup> Thus, our results do not allow us to conclude on this point. Contraction-relaxation coupling under low load (R1) was increased in hamsters with cardiomyopathy in comparison with controls, suggesting an impairment of SR function, as previously reported.<sup>30</sup>

#### EFFECTS OF KETAMINE ON PAPILLARY MUSCLE FROM HAMSTERS WITH CARDIOMYOPATHY

Because of the dual action of ketamine on cardiac muscle, *i.e.*, increased sarcolemmal  $\text{Ca}^{++}$  influx and decreased SR function, and because of the various pathologic changes observed in the myocardium of hamsters with cardiomyopathy, it was not easy to predict the precise mechanical effects of ketamine on this diseased myocardium. This is corroborated by other experimental studies.<sup>34,35</sup> Although the amplitude of the positive inotropic effects of isoproterenol and ouabain has not been found to be different in normal hamsters and those with cardiomyopathy, norepinephrine induced an enhanced response in hamsters with cardiomyopathy in comparison with controls.<sup>35</sup> The effects of compounds with anticalmodulin properties such as perhexiline and bepridil HCl, on the  $\text{Ca}^{++}$  sensitivity of myofilaments, were different in normal hamsters and those with cardiomyopathy.<sup>34</sup>

Our study clearly demonstrated that the positive inotropic effect of ketamine was either markedly decreased or suppressed on cardiomyopathic muscles as shown by the only slight increase in maximum unloaded shortening velocity ( $V_{\max}$ ) with  $10^{-5}$  M ketamine, which was not observed with  $10^{-4}$  M ketamine, and by the lack of increase both in active isometric force (AF/s) (fig. 1) and in peak power output ( $\dot{E}_{\max}$ ) (table 4). Consequently, the shift to the right of the force-velocity curve was nonsignificant (fig. 2). Three hypotheses may explain why ketamine did not induce a positive inotropic effect in hamsters with cardiomyopathy: 1) ketamine did not increase  $\text{Ca}^{++}$  influx; 2) ketamine increased  $\text{Ca}^{++}$  influx but this increase did not result in an increase in contractility; 3) ketamine induced a marked depression of SR function, which counterbalanced the increase in  $\text{Ca}^{++}$  influx.

Ketamine had the same effects on contraction-relaxation coupling under low load (increase in R1) on papillary muscles from normal hamsters and those with cardiomyopathy (fig. 3). Our study therefore suggests that ketamine impaired SR function to a similar extent in the two groups. Nevertheless, as SR function was already impaired in cardiomyopathic muscles, as shown by a higher control value of R1, the consequences of a similarly proportional effect of ketamine on SR function might be different in the two groups. There is a relationship between contractility and relaxation,<sup>15</sup> and it has been shown that the consequences of a decrease in SR function on cardiac contractility depend on the initial SR status. In rat cardiac hypertrophy, impairment of contraction is proportional to alterations in relaxation, so coefficient R1 remains constant.<sup>13</sup> Conversely, in guinea pig cardiac hypertrophy, alterations in relaxation are much more marked than those of contraction,<sup>36</sup> probably because of lower SR function under control conditions in guinea pigs (Fabiato A, personal communication) than in rats.<sup>24</sup> Thus, the effect of ketamine on SR function can partly account for the difference in the inotropic effect of ketamine on normal and cardiomyopathic muscles. Our study cannot conclude about the other two hypotheses that ketamine either did not increase  $\text{Ca}^{++}$  influx or that the increase in  $\text{Ca}^{++}$  influx was not associated with an increase in myocardial performance. However, it has been shown that increasing  $\text{Ca}^{++}$  from 2.5 to 7.5 mM in papillary muscles from normal hamsters and those with cardiomyopathy results in different effects: the enhancement of force was markedly less pronounced (but significant) in cardiomyopathic muscles than in normal muscles (Antony I, Lecarpentier Y, personal communication). Because it has been shown that there is an increase in the voltage-dependent  $\text{Ca}^{++}$  channel density in hamster with cardiomyopathy,<sup>28</sup> the  $\text{Ca}^{++}$  influx might be maximum and could not be increased by ketamine.

Thus, our results suggest that: 1) ketamine does not increase  $\text{Ca}^{++}$  influx (or this increase does not enhance the myocardial performance) in cardiomyopathic muscles; 2) the imbalance between a lower increase in  $\text{Ca}^{++}$  influx and a decrease in SR function (which is already impaired) is responsible for the suppression of the positive inotropic effect of ketamine on cardiomyopathic muscles.

#### RELEVANCE OF THE STUDY

The precise clinical relevance is not clear, as this study was performed *in vitro* at 29° C with a low stimulation rate. Moreover, we only studied the effects of ketamine on the intrinsic mechanical properties of isolated cardiac muscle. Because the cardiovascular effects of ketamine also involve its sympathomimetic effects<sup>2,3</sup> and direct va-

sodilation,<sup>4</sup> further *in vivo* studies are required to assess the effect of ketamine on the entire cardiovascular system during cardiomyopathy.

The results obtained in this experimental model of genetically induced cardiomyopathy cannot be generalized to all types of cardiac failure, especially those related to either pressure and/or volume overload. Nevertheless, hamsters with cardiomyopathy may be considered to be a suitable model of human cardiomyopathy with progressive cardiac failure over a prolonged period, as is observed either in dilated or hypertrophic cardiomyopathies. The experimental model used in the present study was characterized by a moderate decrease in contractility associated with alterations in the relaxation phase, which are known to often precede alterations in the contraction phase in human cardiomyopathies.<sup>37</sup> Moreover, this genetically transmitted disease, which involves both skeletal and cardiac muscle, also partly mimics muscular dystrophy in humans. Management of anesthesia in patients with muscular dystrophy is difficult because of the impairment in respiratory muscle function and decrease in cardiac performance.<sup>38</sup> Even asymptomatic patients are assumed to suffer some degree of cardiomyopathy. Moreover, myocardial depression caused by volatile anesthetics may be enhanced in patients with muscular dystrophy.<sup>39</sup> Our study shows that, although ketamine does not induce a positive inotropic effect, it does not induce a negative inotropic effect on papillary muscles from hamsters with cardiomyopathy. This result may be useful, as most other anesthetics depress myocardial function.<sup>40</sup> In addition, despite the fact that the effect of ketamine on the relaxation phase was similar on papillary muscles from cardiomyopathic and normal hamsters, our study suggests that the consequences of this lusitropic effect might be different because of pre-existing alterations in the relaxation phase in hamsters with cardiomyopathy. It may again be pointed out that other anesthetics, unlike ketamine, induce a marked negative lusitropic effect.<sup>41</sup>

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