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

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Background: **Etomidate has been shown to induce no significant inotropic effect on normal myocardium, but its effects on diseased myocardium remain unknown.**

Methods: **The effects of etomidate (1 and 5 μg/ml) on the intrinsic contractility of left ventricular papillary muscle from normal hamsters and those with cardiomyopathy (strain BIO 82.62, 6 months old) were investigated *in vitro* (Krebs-Henseleit solution, 29° C, pH 7.40, Ca^{++} 2.5 mM, stimulation frequency 3/min).**

Results: **The contractility of papillary muscles from hamsters with cardiomyopathy was less than that of controls, as shown by the decrease in maximum shortening velocity (−25%, $P < .001$), isometric active force (−45%, $P < .01$), peak power output (−57%, $P < .01$), and sarcoplasmic reticulum function ($P < .01$). Etomidate did not induce a significant inotropic effect, as shown by the absence of changes in maximum shortening velocity and active isometric force, except at 5 μg/ml in cardiomyopathic hamsters (+8 ± 10%, $P < .05$). The effects of etomidate on these inotropic parameters were not different in normal and cardiomyopathic hamsters. Etomidate impaired contraction-relaxation coupling under low load in both groups, suggesting that etomidate decreased sarcoplasmic function. This impairment was less ($P < .02$) pronounced in cardiomyopathic muscles. The effects of etomidate on contraction-relaxation coupling under heavy load were not different between groups. In both groups, etomidate had no effect on the peak power output and the curvature of the total force-velocity curve, suggesting that it did not modify the muscle myothermal economy.**

Conclusions: **Etomidate had only a slight effect on the intrinsic mechanical properties of hamster cardiac papillary muscles, and these effects did not depend on the pathophysiologic state of the myocardium. These results may be clinically useful as, unlike etomidate, most anesthetics depress myocardial contractility. (Key words: Anesthetics, intravenous: etomidate. Heart: cardiomyopathy. Heart, papillary muscle: contractility; relaxation.)**

ETOMIDATE is a short-acting intravenous anesthetic associated with no significant cardiovascular depression during induction of anesthesia in humans studies.[1] We recently demonstrated that etomidate has no significant inotropic effect on isolated rat cardiac papillary muscle.[2] However, etomidate slightly impairs the sarcoplasmic reticulum (SR) function, and this impairment is related to the effects of the solvent, propylene glycol.[2] Etomidate in propylene glycol is the preparation used for the induction of anesthesia, which represents a critical period as regards the cardiovascular disturbances induced. As our previous experimental study[2] was conducted on normal myocardium, we sought to determine whether etomidate still has no significant inotropic effect on diseased myocardium, since the effects of etomidate in propylene glycol may differ in the diseased myocardium in which the SR function is modified already.[3] It has been demonstrated that the direct mechanical effects of anesthetic agents, such as ketamine, may differ in normal and diseased myocardium.[4]

The various strains of Syrian hamsters with hereditary cardiomyopathy offer an opportunity to investigate the effects of anesthetic agents on intrinsic myocardial contractility.[4] Indeed, contractility, cellular biochemistry, and physiology have been studied extensively in this model. The time course of cardiac failure is well

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known, and impairment in contractility is primarily due to cardiac muscle cell disease, and therefore may be more relevant to clinical cardiomyopathies.[5,6] The *in vitro* experimental model used in the present study can determine the effects of etomidate on cardiac muscle more completely than simply noting the direction and magnitude of changes produced in the strength of contraction (*i.e.*, changes in the fundamental intrinsic mechanical properties of cardiac muscle: contraction, relaxation, contraction-relaxation coupling, and energetics). We therefore conducted an *in vitro* study on the effects of etomidate on intrinsic contractility of cardiac papillary muscles from normal hamsters and those with cardiomyopathy.

Materials and Methods

Animals

Five normal Syrian hamsters and six Syrian hamsters with cardiomyopathy (strain BIO 82.62) were used in this study (Charles River, France). In this strain, all animals of both sexes develop cardiomyopathy from the age of 6 weeks but without cardiac hypertrophy.[4,7] Care of the animals conformed to the recommendations of the Helsinki Declaration, and the study was performed in accordance with the regulations of the official edict of the French Ministry of Agriculture. All animals were aged 6 months. Body weight and heart weight were determined at the moment of killing.

Experimental Protocol

Twenty-two left ventricular papillary muscles (2 from each hamster) were studied. After brief anesthesia with ether, the hearts were removed quickly and papillary muscles were carefully excised and suspended vertically in a 60-ml Krebs-Henseleit bicarbonate buffer solution containing (mM) 118 NaCl, 4.7 KCl, 1.2 $MgSO_4$, 1.1 KH_2PO_4, 25 $NaHCO_3$, 2.5 $CaCl_2$, and 4.5 glucose. Preparations were field-stimulated at 3/min by two platinum electrodes with rectangular wave pulses (5 ms) just above threshold. This stimulation frequency corresponds to the apex of the force-frequency relationship. The bathing solution was bubbled with 95% O_2 plus 5% CO_2, giving a pH of 7.40, and the temperature was maintained at 29° C. After a 1-h stabilization period at the initial muscle length at the apex of the length-active isometric tension curve (L_{max}), papillary muscles recovered their optimal mechanical performance, which remained stable for many hours. Table 1 summarizes the muscle characteristics during control conditions at L_{max}.

Control values of each mechanical parameter were recorded, and etomidate in propylene glycol (Hypnomidate®, Janssen, Boulogne, France) was then added to the bathing solution. Two concentrations of etomidate were tested in a cumulative manner: 1 μg/ml (4 μM) and 5 μg/ml (20 μM). Concentrations of etomidate during anesthesia range from 0.2 to 2 μg/ml;[8] these two concentrations were tested previously in normal rat myocardium.[2]

At the end of the study, the cross-sectional area was calculated from the length and weight of papillary muscle, assuming a muscle density of 1.

Electromagnetic Lever System and Recording

The electromagnetic lever system has been described.[9] Briefly, the load applied to the muscle was determined by means of a servomechanism-controlled current through the coil of an 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 of force and length obtained with a computer, as previously described.[2] The recording speed was one A/D (12 bits) conversion every 1 ms, for a total recording time of 500 ms.

Mechanical Parameters

Conventional mechanical parameters at L_{max} were calculated from three 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; the muscle was released from preload to zero-load with a critical damping

Table 1. Characteristics of Papillary Muscles of Normal Hamsters and Those with Cardiomyopathy

Hamsters	L_{max} (mm)	CSA (mm^2)	RF/TF
Normal	4.4 ± 1.0	0.94 ± 0.09	0.12 ± 0.06
(n = 10)	(2.5–5.5)	(0.80–1.00)	(0.08–0.28)
Cardiomyopathy	3.3 ± 0.8*	0.98 ± 0.17	0.19 ± 0.07*
(n = 12)	(2.0–5.0)	(0.80–1.15)	(0.08–0.31)

Values are mean ± SD, with range in parentheses. L_{max} = initial length; CSA = cross-sectional area; RF/TF = ratio of resting force to total force.

* $P < .05$.

to decrease the first and rapidly shortening overshoot resulting from the recoil of series passive elastic components, as previously reported;[10] the maximum unloaded shortening velocity (V_{max}) was determined from this twitch. The third twitch was fully isometric at L_{max}.

The mechanical parameters characterizing the contraction (inotropy) and relaxation (lusitropy) phases and coupling between contraction and relaxation are defined as follows:

Contraction Phase. We determined V_{max} using the zero-load clamp technique,[10] the maximum shortening velocity ($_{max}Vc$) of the twitch with preload only, the maximum isometric active force normalized per cross-sectional area (AF), and the peak of the positive force derivative normalized per cross-sectional area ($+dF \cdot dt^{-1}$). Active force is the total force less the resting force (preload). The maximum unloaded shortening velocity and AF tested the inotropic state of papillary muscle under low and high load respectively.

Relaxation Phase. We determined the maximum lengthening velocity ($_{max}Vr$) of the twitch with preload only, and the peak of the negative force derivative normalized per cross-sectional area ($-dF \cdot dt^{-1}$). These two parameters tested the lusitropic state of papillary muscle under low load and high load, respectively. However, since the relaxation phase depends on the contraction phase, variations of contraction and relaxation must be considered simultaneously to quantify the drug-induced changes in relaxation. Therefore, indexes that test the contraction-relaxation coupling have been developed.[11]

Contraction-Relaxation Coupling. Coefficient R1 ($_{max}Vc/_{max}Vr$) 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.[12] Due to the lower affinity of cardiac muscle troponin for calcium when it is rapidly shortening under low load,[13] relaxation proceeds more rapidly than contraction, apparently because of the rapid SR uptake of calcium. Thus, R1 is significantly less than 1 and tests SR function. Coefficient R2 $[(+dF \cdot dt^{-1})/(-dF \cdot dt^{-1})]$, tests the coupling between contraction and relaxation under high load. When muscle is contracting isometrically, sarcomeres shorten to a lesser extent.[12] Due to a higher affinity of cardiac muscle troponin for calcium, relaxation is determined primarily by unbinding of calcium, not by SR function. Thus, R2 is greater than 1 and reflects myofilament calcium sensitivity.

Energetic Parameters

The force-velocity curve was derived from the peak shortening velocity (V) of seven to nine afterloaded twitches plotted against the total force normalized per cross-sectional area (TF) and from that of the zero-load clamp twitch, as previously described.[2,14] The following energetic parameters were derived from the Hill's equation[15] of the hyperbola (TF/V relationship): the peak power output ($\dot{E}_{max}$) and curvature of the hyperbola (G). The curvature of the force-velocity relationship has been shown to be linked to the myothermal economy and cross-bridge kinetics[14,16]: 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 higher muscle efficiency.[14,16]

Statistical Analysis

Data were expressed as mean ± SD. Control values in normal hamsters and those with cardiomyopathy were compared by means of the Student's *t* test. The effects of etomidate in normal hamsters and those with cardiomyopathy were compared by repeated-measures two-way analysis of variance and the Newman-Keuls test. To determine the parameters of the Hill's equation, multiple linear regression was performed using the least squares method, as previously described.[2,14] All *P* values were two-tailed and a *P* value less than .05 was necessary to reject the null hypothesis. Statistical analysis was performed on a personal computer using PCSM® software (Deltasoft, Meylan, France).

Results

Body weight (126 ± 7 g) and heart weight (480 ± 6 mg) of normal hamsters were not significantly different from those of hamsters with cardiomyopathy (111 ± 7 g and 446 ± 26 mg, respectively); cardiomyopathy occurred with no cardiac hypertrophy, as shown by the lack of significant increase in the heart weight/body weight ratio in cardiomyopathic hamsters ($4.03 \pm 0.17 \times 10^{-3}$) as compared to normal hamsters ($3.85 \pm 0.36 \times 10^{-3}$).

The intrinsic mechanical performance of papillary muscles from hamsters with cardiomyopathy was significantly lower during the isometric (AF, $+dF \cdot dt^{-1}$) and the isotonic (V_{max}, $_{max}Vc$) twitches (table 2). The two parameters that test the contraction-relaxation

Table 2. Mechanical Parameters of Papillary Muscle of Normal Hamsters and Those with Cardiomyopathy

Parameters	Normal (n = 10)	Cardiomyopathy (n = 12)	P
Contraction			
V_{max} ($L_{max} \cdot s^{-1}$)	3.63 ± 0.50	2.74 ± 0.50	.001
$_{max}Vc$ ($L_{max} \cdot s^{-1}$)	2.46 ± 0.45	1.80 ± 0.51	.01
AF ($mN \cdot mm^{-2}$)	47 ± 20	26 ± 15	.01
$+dF \cdot dt^{-1}$ ($mN \cdot s^{-1} \cdot mm^{-2}$)	555 ± 209	340 ± 188	.01
Relaxation			
$_{max}Vr$ ($L_{max} \cdot s^{-1}$)	3.08 ± 0.67	2.08 ± 0.72	.01
$-dF \cdot dt^{-1}$ ($mN \cdot s^{-1} \cdot mm^{-2}$)	318 ± 146	215 ± 117	NS
Contraction–relaxation coupling			
R1 (low load)	0.80 ± 0.05	0.90 ± 0.12	.02
R2 (high load)	1.80 ± 0.32	1.58 ± 0.13	.05

Values are mean ± SD. V_{max} = maximum unloaded shortening velocity; $_{max}Vc$ = maximum shortening velocity; AF = isometric active force normalized per cross-sectional area (CSA); $+dF \cdot dt^{-1}$ = peak of the positive force derivative normalized per CSA; $_{max}Vr$ = maximum lengthening velocity; $-dF \cdot dt^{-1}$ = peak of the negative force derivative normalized per CSA; R1 = $_{max}Vc/_{max}Vr$; R2 = $\cdot dF \cdot dt^{-1}/-dF \cdot dt^{-1}$.

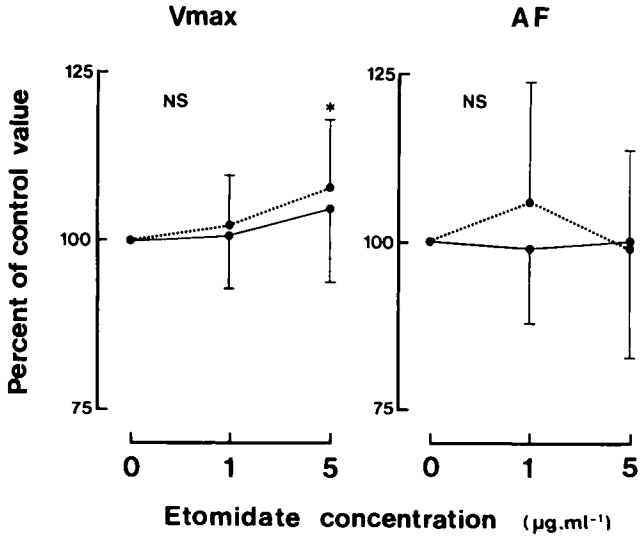

Fig. 1. Comparison of inotropic effects of etomidate on maximum unloaded shortening velocity ($\dot{V}_{max}$) and active force normalized per cross-sectional area (AF) of papillary muscles of normal hamsters (solid line) and those with cardiomyopathy (dotted line). Data are mean ± SD. Between-group differences were not significant (NS). *$P < .05$ *versus* control values.

coupling under low (R1) and heavy (R2) load were different: for cardiomyopathic muscles, R1 was higher whereas R2 was lower than for normal muscles (table 2). The peak power output was lower for cardiomyopathic muscles, as well as for G (table 3).

Etomidate (1 and 5 μg/ml) induced no significant inotropic effect on normal muscles as shown by the absence of changes in V_{max} and the active isometric force (fig. 1). No differences in these inotropic parameters were observed between normal and cardiomyopathic hamsters, but a significant increase in V_{max} was noted at 5 μg/ml etomidate in cardiomyopathic muscles (fig. 1).

A negative lusitropic effect, *i.e.*, a less rapid relaxation, was observed in normal muscles under low load (decrease in $_{max}Vr$; fig. 2), which was significant only at 5 μg/ml etomidate. In contrast, no significant decrease in $_{max}Vr$ was noted in cardiomyopathic muscles (fig. 2). Etomidate impaired contraction-relaxation coupling under low load (increase in R1) in both groups, but this impairment was less pronounced in cardiomyopathic muscles (fig. 2). In contrast, no significant lusitropic effects (changes in $-dF \cdot dt^{-1}$) were observed with etomidate under high load in both groups (fig. 3). Under high load, etomidate induced a slight increase in R2 that was only significant at 5 μg/ml etomidate in normal muscles; however, no differences in the contraction-relaxation coupling under high load were noted between the two groups.

Table 3. Effects of Etomidate on the Energetic Parameters of Papillary Muscles from Normal Hamsters and Those with Cardiomyopathy

Parameter	Hamster	Control	Etomidate 1 μg·ml⁻¹	Etomidate 5 μg·ml⁻¹
$\dot{E}_{max}$ ($mN \cdot L_{max} \cdot s^{-1} \cdot mm^{-2}$)	Normal	30 ± 9	30 ± 11	31 ± 12
	Cardiomyopathic	13 ± 7*	14 ± 7	13 ± 7
G	Normal	2.83 ± 1.22	2.71 ± 0.26	2.74 ± 0.27
	Cardiomyopathic	1.80 ± 0.45*	1.88 ± 0.54	1.90 ± 0.55

Values are mean ± SD. G = curvature of the force–velocity hyperbola; $\dot{E}_{max}$ = peak power output.

* $P < .01$ *versus* normal muscles. With etomidate, no differences *versus* control values were significant.

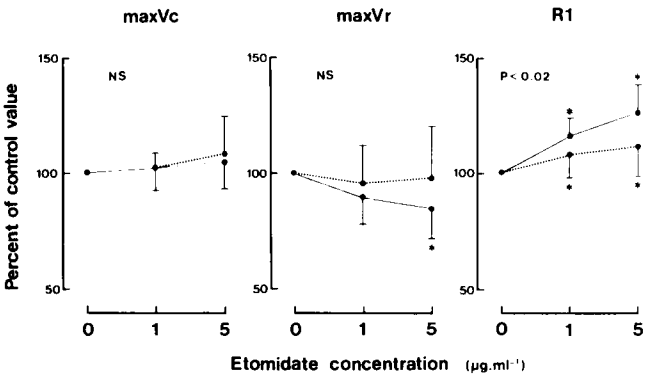

Fig. 2. Comparison of the effects of etomidate on maximum shortening velocity ($_{max}$Vc), lengthening velocity ($_{max}$Vr), and contraction-relaxation coupling under low load (R1 = $_{max}$Vc/$_{max}$Vr of papillary muscles of normal hamsters (solid line) and those with cardiomyopathy (dotted line). Data are mean ± SD. The *P* value concerns the between-group differences. **P* < .05 *versus* control values.

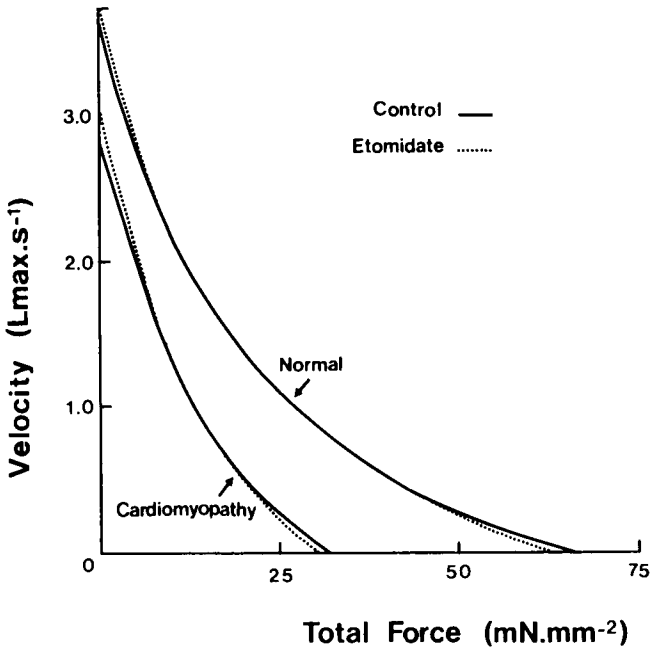

Fig. 4. Effects of etomidate (5 μg/ml) on the total force-velocity relationship of papillary muscles of normal hamsters and those with cardiomyopathy.

The peak power output and G of normal and cardiomyopathic muscles were not modified after exposure to etomidate (table 3). As shown in figure 4, the force-velocity curve was not shifted by etomidate in both groups.

Discussion

Cardiomyopathy in Syrian hamsters is characterized by the progressive occurrence of focal myocardial degeneration, fibrosis, and calcification during the life of the animal.[5,6] At age 30–40 days, histologic lesions become apparent and myocardial performance decreases.

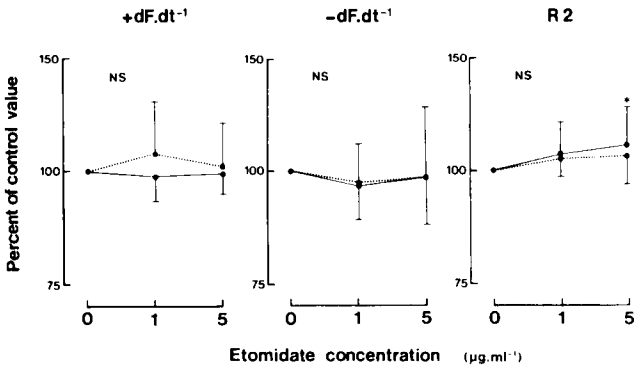

Fig. 3. Comparison of the effects of etomidate on maximum increase ($+dF \cdot dt^{-1}$) and decrease ($-dF \cdot dt^{-1}$) of the isometric force and contraction-relaxation coupling under high load [R2 = $(+dF \cdot dt^{-1})/(-dF \cdot dt^{-1})$] of papillary muscles of normal hamsters (solid line) and those with cardiomyopathy (dotted line). Data are mean ± SD. Between-group differences were not significant (NS). **P* < .05 *versus* control values.

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 AF, V_{max}, and $\dot{E}_{max}$. Moreover, the decreased G suggests that cardiac muscle efficiency was lower in cardiomyopathic hamsters, as previously described.[17] The decreased myocardial performance in cardiomyopathic hamsters may be explained by: 1) the decrease in the activity of G regulatory proteins[18]; 2) decreased sarcolemmal Ca^{++} and Na^{+}-K^{+} ATPAse activities[19]; 3) modification of conductance[20] and/or density[21] of voltage-sensitive calcium channels; 4) alterations in the creatine kinase system[22]; 5) decrease in SR function[23]; and 6) modification of the sensitivity of myofilaments to calcium,[22] with alteration of the regulatory proteins of the thin filaments (troponin and tropomyosin)[24] and isomyosin shift from the V1 toward the V3 type (which has the lowest ATPase activity).[25] A recent study supports the hypothesis of microvascular spasm leading to focal injury.[26] This is considered to be a valuable experimental model for studying cardiomyopathy that results in progressive cardiac failure over a prolonged period of time, as in humans.

R1 was increased in hamsters with cardiomyopathy in comparison with controls, suggesting an impairment of SR function, as previously reported.[4,23] R2 of cardiomyopathic muscles was lower than that of the controls, suggesting that myofilament calcium sensitivity was lower in hamsters with cardiomyopathy, as previously reported.[4] However, previous studies gave conflicting results on changes in the calcium sensitivity of myofilaments in the hamsters with cardiomyopathy.[22,27]

Because of the complex action of anesthetic agents on cardiac muscle[28] and because of the various pathologic changes observed in the myocardium of cardiomyopathic hamsters, it is not easy to predict the precise mechanical effects of anesthetic agents on this diseased myocardium. Indeed, it has been demonstrated that the inotropic effect of ketamine[4] may differ in normal and cardiomyopathic hamsters. In normal muscle, etomidate induced no significant inotropic effect as shown by the lack of significant changes in active isometric force (fig. 1) and peak power output (table 3). These results with hamster myocardium are consistent with our previous findings in rat myocardium.[2] Nevertheless, in rat myocardium, a slight but significant increase in V_{max} was observed, suggesting that etomidate has a direct effect on cross-bridge kinetics.[2] Such a moderate increase in V_{max} was noted in cardiomyopathic muscles only at the highest concentration of etomidate (fig. 1). However, no differences in the inotropic effects of etomidate were noted between normal hamsters and those with cardiomyopathy.

In normal muscles, etomidate decreased $_{max}$Vr and did not change $_{max}$Vc, resulting in an impairment in contraction-relaxation coupling under low load (increase in R1; fig. 2). Under low load, the SR appears to play a major role in the regulation of isotonic relaxation. The increase in R1 observed with etomidate therefore suggests a decrease in SR function, as observed previously in rat myocardium.[2] The increase in R1 with 1 and 5 μg/ml etomidate was lower in hamsters (+16% and +26%, respectively) than in rats (+47% and +43%, respectively).[2] This result was not surprising since SR function in rat myocardium, and particularly the calcium-induced calcium release, is very high.[29] It has been shown that the impairment of SR function observed with etomidate is related mainly to its solvent, propylene glycol.[2] In the current study, no attempt was made to separate the effects of the solvent from those of etomidate, since these two compounds are mixed in the preparation used for induction of anesthesia, which actually represents the critical period as regards the extent of cardiovascular disturbances induced. Etomidate also impaired contraction-relaxation coupling under low load in papillary muscles from cardiomyopathic hamsters, but this impairment was less pronounced than that of normal hamsters (fig. 2). Thus, despite the fact that SR function was already impaired in cardiomyopathic muscles (table 1), the consequences of etomidate on SR function probably were less pronounced in this group.

Etomidate did not modify $\dot{E}_{max}$ and G in both groups. The peak power output is considered to be the most robust parameter for signalling changes in muscle activation.[30] Hill's hyperbola has been shown to be linked to myothermal economy and cross-bridge kinetics[14,16]: the higher value of G, the higher the muscle efficiency. Despite the fact that myothermal economy was decreased in cardiomyopathic muscles, as shown by a lower value of G, etomidate had no effect on myothermal economy in cardiomyopathic muscles.

In both groups, etomidate did not modify $+dF \cdot dt^{-1}$ and $-dF \cdot dt^{-1}$. A slight increase in R2 was noted in normal muscles, reaching statistical significance only at 5 μg/ml etomidate. An increase in R2 suggests an increase in calcium myofilament sensitivity.[11] Nevertheless, this effect was moderate, and whereas no changes occurred in $+dF \cdot d^{-1}$, the significant increase in R2 was not related to a decrease in $-dF \cdot dt^{-1}$. Consequently, this result must be interpreted with caution, concerning the effects of etomidate on calcium myofilament sensitivity. However, no differences were observed between groups.

Some remarks must be included to minimize the clinical relevance of our results. First, this study was performed *in vitro* at 29° C with a low stimulation rate; however, papillary muscles must be studied at this temperature because stability of mechanical parameters is not sufficient at 37° C and at low frequency because high stimulation frequency induces core hypoxia.[31] Second, we only studied the effects of etomidate on the intrinsic mechanical properties of isolated cardiac muscle; thus, further *in vivo* studies are required to assess the effect of etomidate on the entire cardiovascular system during cardiomyopathy. Third, in 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; whereas in human myo-

cardium, a positive staircase is observed and the myosin isoforms are predominantly of the V3 type. Thus, the inotropic effect of etomidate on human myocardium remains speculative at present. Fourth, the results obtained in this experimental model of genetically induced cardiomyopathy cannot be generalized to all types of cardiac failure. Nevertheless, hamsters with cardiomyopathy may be considered a suitable model of human cardiomyopathy with progressive cardiac failure over a prolonged period as is observed either in dilated or hypertrophic cardiomyopathies. Furthermore, because about 75% of etomidate is protein bound and because the bathing solution was protein-free, the concentrations tested in the present study might be considered high (respectively, 2 and 10 times the maximum therapeutic concentration of free etomidate), suggesting that at lower concentrations there would be less or no effect of etomidate.

Our study showed that etomidate had only slight effects on the intrinsic mechanical properties of cardiac papillary muscles from normal and cardiomyopathic hamsters. This result may be useful as most other anesthetics depress myocardial function.[28,32] Etomidate slightly impairs the SR function, but this impairment is even less pronounced in cardiomyopathic hamsters. However, the possible consequences of this slight impairment in relaxation remain speculative concerning the whole heart mechanics, and further *in vivo* studies are needed.

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