In Vitro Effects of Etlanolone on Rat Myocardium

Bruno Riou, M.D., Ph.D., Patrick Ruel, M.D., Jean-Luc Hanouz, M.D., Olivier Langeron, M.D., Yves Lecarpentier, M.D., Ph.D., Pierre Viars, M.D.

Background: Etlanolone is a new short-acting intravenous induction agent. However, its effects on intrinsic myocardial contractility remain unknown.

Methods: The effects of etanolone and its solvent (soya bean emulsion) on the intrinsic contractility of rat left ventricular papillary muscles were investigated in vitro (Kreb's-Henseleit solution, 29°C, pH 7.40, CaCl2 0.5 mM, stimulation frequency 12 pulses/min). We studied contraction, relaxation, contraction-relaxation coupling under high and low load, and postrest potentiation.

Results: Etlanolone (0.1, 0.3, 1, 3, and 10 µg⋅ml⁻¹) induced no significant inotropic effect, as shown by the lack of changes in maximum unloaded shortening velocity and active isotropic force. Etlanolone did not significantly modify the contraction-relaxation coupling under low load, suggesting that it did not modify calcium uptake by the sarcoplasmic reticulum. Etlanolone did not significantly modify the contraction-relaxation coupling under high load, suggesting that it did not modify calcium myofilament sensitivity. Etlanolone decreased the postrest potentiation in a concentration-dependent manner (from 150 ± 14% to 118 ± 9% at 10 µg⋅ml⁻¹, P < 0.001), suggesting a decrease in the maximum capacity of calcium release by the sarcoplasmic reticulum, whereas its solvent did not. However, etanolone did not slow postrest potentiation recovery, as shown by the absence of significant changes in the recovery slope (4.5 ± 1.4 vs. 3.8 ± 1.0 beats, difference not statistically significant).

Conclusions: Etlanolone induced no significant inotropic effect on rat myocardium. It induced a decrease in the calcium release capacity of the sarcoplasmic reticulum, but this effect was not sufficiently important to modify the inotropic properties. (Key words: Anesthetics, intravenous: etanolone. Heart, papillary muscle: contractility; relaxation.)

ELTANOLONE is a new short-acting intravenous anesthetic agent that is now undergoing clinical investigation. It is a naturally occurring metabolite of progesterone that has been shown to be 3.2 times more potent than profolol and 6 times more potent than thiopental. The cardiovascular effects of etanolone have still not been fully defined. The decrease in arterial blood pressure produced by etanolone has been shown to be less than that after an equipotent dose of profolol. However, the effects of etanolone on intrinsic myocardial contractility remain unknown. Because of the shortcomings in preload, systemic resistance, sympatoactivity, and central nervous system activity, the exact effects of anesthetic agents on intrinsic myocardial contractility are difficult to assess in vivo. Therefore, we therefore conducted an in vitro study of the effects of etanolone on rat left ventricular papillary muscle contractility. The experimental model used in the current study enabled us to determine the effects of etanolone on the mechanics and energetics of cardiac muscle. Because etanolone is available in an emulsion media, we studied the effects of etanolone in its solvent and those of the solvent alone on rat myocardium.
EFFECTS OF ELTANOLONE ON RAT MYOCARDIUM

Materials and Methods

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.

Experimental Protocol

After brief anesthesia with ether, the hearts were quickly removed from adult male Wistar rats (Ifla Credo, France), weighing 250–300 g. Left ventricular papillary muscles were carefully excised and suspended vertically in a 200-ml jacketed reservoir with Krebs-Henseleit bicarbonate buffer solution containing (mm) 118 NaCl, 4.7 KCl, 1.2 MgSO₄, 1.1 KH₂PO₄, 25 NaHCO₃, 2.5 CaCl₂, and 4.5 glucose. The Krebs-Henseleit solution was prepared daily with highly purified water (Ecopure, Barnstead/Thermolyne Corporation, Dubuque, IA). The jacketed reservoir was maintained at 29°C with a thermostatic water circulator (Polystat 5HP, Bioblock, Illkirch, France) with continuous monitoring of the solution temperature with a temperature probe (PT100, Bioblock). Preparations were field-stimulated at 12 pulses/min by two platinum electrodes with rectangular wave pulses of 5 ms duration just above threshold. The bathing solution was bubbled with 95% oxygen–5% carbon dioxide, resulting in a pH of 7.40. After a 60-min stabilization period at the initial muscle length at the apex of the length-active isometric tension curve (Lₘₐₓ) papillary muscles recovered their optimal mechanical performance, which remained stable for many hours. Suitable preparations were selected as previously described.  

The control values of each mechanical parameter were recorded. Then, the extracellular calcium concentration ([Ca²⁺]ₑ) was decreased from 2.5 to 0.5 mm. [Ca²⁺]ₑ was decreased because rat myocardial contractility is nearly maximum at 2.5 mm, and consequently it is difficult to quantify a positive inotropic effect without previously decreasing [Ca²⁺]ₑ. Moreover, in rat myocardium, a postrest potentiation study is more sensitive at low [Ca²⁺]ₑ. Because etanolon is insoluble in aqueous media, we tested the pharmacological form of etanolon in which a soya bean emulsion (Intralipid) is the solvent (Pharmacia, Stockholm, Sweden) (etanolon group, n = 10). Concentrations of etanolon during anesthesia ranged from 0.5 to 3 μg·mL⁻¹. Etanolon is highly bound (99%) to plasma protein, but this does not seem to influence its rapid disappearance from the blood and extensive tissue distribution. Thus, five concentrations of etanolon were tested in a cumulative manner: 0.1 μg·mL⁻¹ (0.31 μM), 0.3 μg·mL⁻¹ (0.94 μM), 1 μg·mL⁻¹ (3.14 μM), 3 μg·mL⁻¹ (9.42 μM), and 10 μg·mL⁻¹ (31.40 μM), with a 15 min period between each additional dose. Indeed, a preliminary study showed that the effects of the highest dose (10 μg·mL⁻¹) of etanolon remained stable between 15 to 60 min. In the solvent group (n = 8), the solvent alone (Pharmacia) was tested at five concentrations, corresponding to those tested in the etanolon group and according to the same cumulative manner. Last, because of the long duration of the protocol, a control group (n = 8) was also studied.

The etanolon solvent modifies the physical properties of the bathing solution and probably increases its surface tension, slightly modifying papillary muscle oxygenation, which could be critical when studying papillary muscle mechanics. Although the etanolon pharmaceutical preparation has a pH of 8.0, addition of either etanolon (10 μg·mL⁻¹) in its solvent (n = 7) or its solvent alone (n = 8) did not significantly alter the pH or the partial pressures of oxygen and carbon dioxide in the Krebs-Henseleit solution.

Electromagnetic Lever System and Recording

The electromagnetic lever system has been previously described. In brief, 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.

Mechanical Parameters

Conventional mechanical parameters at Lₘₐₓ were calculated from three twitches. The first twitch was isometric and was loaded with the preload corresponding to Lₘₐₓ. 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 to slow the first and rapid shortening overshoot resulting from the recoil of series passive elastic components, as previously reported; the maximum unloaded shortening velocity (Vₘₐₓ) was determined from this twitch. The third twitch was fully isometric at Lₘₐₓ. The mechanical parameters characterizing the

Anesthesiology. V 83, No 4, Oct 1995
contraction and relaxation phases, and the contraction-relaxation coupling are defined as follows (fig. 1).

**Contraction Phase.** We determined $V_{\text{max}}$ using the zero-load clamp technique: maximum shortening velocity of the twitch with preload only; maximum isometric active force normalized per cross-sectional area (AF); and the peak of the positive force derivative normalized per cross-sectional area ($+\frac{dF}{dt}$). $V_{\text{max}}$ and AF tested the isotropic state under low and high loads respectively. We also determined the time-to-peak shortening and the time-to-peak force in the isotonic and isometric twitches, respectively.

**Relaxation Phase.** We determined maximum lengthening velocity of the twitch with preload only and the peak of the negative force derivative at $l_{\text{max}}$ normalized per cross-sectional area ($-\frac{dF}{dt}$). Because changes in the contraction phase induce coordinated changes in the relaxation phase, variations in contraction and relaxation must be simultaneously considered to quantify drug-induced changes in lusitropy. Indexes of coupling between contraction and relaxation have therefore been developed.

**Contraction-Relaxation Coupling.** Coefficient $R_1$, where $R_1 = V_{\text{max}}$ lengthening velocity/maximum shortening velocity of the twitch with preload only, 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. Because of the lower sensitivity of myofilament for calcium when cardiac muscle is markedly shortened under low load, relaxation proceeds more rapidly than contraction, apparently as a result of the rapid uptake of calcium by the sarcoplasmic reticulum (SR). Thus, in rat myocardium, $R_1$ tests SR function. Coefficient $R_2$ ($+\frac{dF}{dt} / -\frac{dF}{dt}$) tests the coupling between contraction and relaxation under high load. When the muscle contracts isometrically, sarcomeres shorten very little. Because of a higher sensitivity of myofilament for calcium, the time course of relaxation is determined by calcium unbinding from troponin C rather than by calcium sequestration by the SR. Thus, $R_2$ reflects myofilament calcium sensitivity.

**Energetic Parameters**

The force-velocity curve was derived from the peak shortening velocity of seven to nine afterloaded twitches plotted against the total force normalized per cross-sectional area and from that of the zero-load clamp twitch, as previously reported. The following energetic parameters were derived from the Hill's hyperbola equation (relation between total force normalized per cross-sectional area and velocity): the peak power output and the curvature of the force-velocity hyperbola ($G$). $G$ has been shown to be linked to the myothermodynamic efficiency and cross-bridge kinetics: the more curved the hyperbola (i.e., the higher value of $G$), the higher the muscle efficiency. During cardiac hypertrophy, impaired myocardial performance is associated with an increase in $G$ and higher myothermodynamic efficiency. In contrast, chlorpromazine decreases $G$ and thus induces a decrease in myothermal efficiency.

**Postrest Potentiation**

Recovery of a stable, reproducible isometric contraction after a rest interval (1 min) was studied to identify the effects of etanolone on SR functions. During rest in the rat, SR accumulates calcium in addition to that accumulated with regular stimulation, and the force of the first beat after the rest interval (B1) is greater than that of the last beat before the rest interval (B0). During stimulation of the postrest recovery (B1, B2, B3 . . .), the SR-dependent part of activator calcium decreases somewhat toward a steady state, which is reached in few beats. Therefore, the effects of etanolone on the postrest-potentiated contraction may provide insight into the effects of etanolone on SR function.
Table 1. Comparison of the Effects of Eltanolone in Its Solvent (n = 10) and Those of Its Solvent Alone (n = 8) on Intrinsic Mechanical Properties of Rat Left Ventricular Papillary Muscles (Control Group, n = 8)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Control Values</th>
<th>0.1 µg/ml</th>
<th>0.3 µg/ml</th>
<th>1 µg/ml</th>
<th>3 µg/ml</th>
<th>10 µg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>102 ± 8</td>
<td>108 ± 7</td>
<td>110 ± 11</td>
<td>107 ± 8</td>
<td>104 ± 10</td>
</tr>
<tr>
<td></td>
<td>Eltanolone</td>
<td>2.34 ± 0.46</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Solvent</td>
<td>1.94 ± 0.38</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>2.23 ± 0.23</td>
<td>100 ± 6</td>
<td>107 ± 9</td>
<td>110 ± 11</td>
<td>115 ± 8</td>
<td>117 ± 8</td>
</tr>
<tr>
<td></td>
<td>Eltanolone</td>
<td>34 ± 8</td>
<td>102 ± 3</td>
<td>106 ± 6</td>
<td>107 ± 6</td>
<td>107 ± 9</td>
<td>108 ± 8</td>
</tr>
<tr>
<td></td>
<td>Solvent</td>
<td>34 ± 10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>27 ± 13</td>
<td>99 ± 5</td>
<td>104 ± 3</td>
<td>107 ± 6</td>
<td>110 ± 10</td>
<td>100 ± 11</td>
</tr>
<tr>
<td>Contract-relaxation coupling</td>
<td>Eltanolone</td>
<td>0.68 ± 0.09</td>
<td>100 ± 8</td>
<td>100 ± 10</td>
<td>101 ± 11</td>
<td>101 ± 13</td>
<td>104 ± 11</td>
</tr>
<tr>
<td></td>
<td>Solvent</td>
<td>0.67 ± 0.10</td>
<td>102 ± 8</td>
<td>106 ± 16</td>
<td>106 ± 11</td>
<td>108 ± 13</td>
<td>113 ± 18</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>0.75 ± 0.05</td>
<td>100 ± 7</td>
<td>98 ± 9</td>
<td>98 ± 9</td>
<td>100 ± 11</td>
<td>102 ± 12</td>
</tr>
<tr>
<td></td>
<td>Eltanolone</td>
<td>1.68 ± 0.29</td>
<td>97 ± 5</td>
<td>98 ± 14</td>
<td>97 ± 10</td>
<td>99 ± 12</td>
<td>96 ± 10</td>
</tr>
<tr>
<td></td>
<td>Solvent</td>
<td>1.84 ± 0.22</td>
<td>96 ± 7</td>
<td>96 ± 9</td>
<td>95 ± 13</td>
<td>98 ± 6</td>
<td>100 ± 6</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>1.94 ± 0.40</td>
<td>98 ± 5</td>
<td>99 ± 7</td>
<td>101 ± 8</td>
<td>98 ± 7</td>
<td>99 ± 9</td>
</tr>
</tbody>
</table>

Values are mean ± SD. There are no significant differences between groups.

V_max = maximum unloaded shortening velocity; AF = isometric active force normalized per cross-sectional area (CSA); R1 = \( \frac{V_{cm}}{V_r} \); R2 = \( +\delta F/\delta t^1 - \delta F/\delta t^2 \).

The following is the Hill's hyperbolic force-velocity relation: the peak force-velocity relationship is linked to the magnitude of the isometric force decay. The rate constant c of the exponential decay of AF was determined, as previously described. The number of beats required for the postrest contraction to decay to one tenth of its maximum (B1); it is assumed to represent the time required for the SR to reset itself and was therefore used to test SR function. At the end of the study, the muscle cross-sectional area was calculated from the length and weight of papillary muscle, assuming a density of 1.

Statistical Analysis. Data are expressed as mean ± SD. Comparisons of control values between groups were performed using the Student's t test or analysis of variance. Comparison of several means were performed using repeated-measures analysis of variance and Newman-Keuls test. The energetic parameters were derived from the Hill's equation using multilinear regression and the least square method, as previously reported. The beat-to-beat decay of active isometric force during postrest recovery (B1) of contractile machinery, and was estimated using the least square method, as previously described. All P values were two-sided, and a P value of less than 0.05 was required to reject the null hypothesis. Statistical analysis was performed using PC software (Deltofsoft, Meylan, France).

Results

Twenty six left ventricular papillary muscles were used in the current study. The mean cross-sectional area was 0.72 ± 0.16 mm² (range 0.44–1.04), the mean \( L_{max} \) was 4.6 ± 0.9 mm (range 3.0–6.5), the mean ratio of rest to total isometric force was 0.13 ± 0.04 (range 0.08–0.22), R1 was 0.77 ± 0.07 (range 0.61–0.85), and no significant differences were noted between groups. A decrease in contractility was observed as \( [Ca^{2+}]_o \), decreased from 2.5 to 0.5 mm; the decrease in \( V_{max} \) (70 ± 10%) of the value at a \( [Ca^{2+}]_o \) of 2.5 mm and AF (59 ± 11% of the value at a \( [Ca^{2+}]_o \) of 2.5 mm) were consistent with previous reports. Eltanolone induced no significant inotropic changes, as shown by the absence of significant changes in \( V_{max} \) and AF compared with the control group (table 1). The force-velocity relation was not modified by eltanolone and its solvent, as shown by the nonsignificant changes in peak power output and in G (table 2). Eltanolone induced no significant changes in time-to-peak force and time-to-peak shortening (data not shown).

Eltanolone and its solvent did not significantly modify maximum lengthening velocity of the twitch with pre-
Table 2. Comparison of the Effects of Etanolone in Its Solvent (n = 10) and Its Solvent Alone (n = 8) on Energetic Parameters of Rat Left Ventricular Papillary Muscles

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Control (absolute values)</th>
<th>0.1 µg/ml</th>
<th>0.3 µg/ml</th>
<th>1 µg/ml</th>
<th>3 µg/ml</th>
<th>10 µg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>E\textsubscript{max} \ (Joule \cdot m\textsuperscript{2} \cdot s\textsuperscript{-1})</td>
<td>Etanolone</td>
<td>17.0 ± 3.0</td>
<td>99 ± 6</td>
<td>111 ± 6</td>
<td>111 ± 11</td>
<td>117 ± 14</td>
<td>108 ± 15</td>
</tr>
<tr>
<td></td>
<td>Solvent</td>
<td>14.4 ± 4.7</td>
<td>105 ± 21</td>
<td>105 ± 15</td>
<td>112 ± 23</td>
<td>117 ± 20</td>
<td>121 ± 17</td>
</tr>
<tr>
<td>G</td>
<td>Etanolone</td>
<td>2.77 ± 1.16</td>
<td>108 ± 13</td>
<td>104 ± 12</td>
<td>103 ± 21</td>
<td>100 ± 23</td>
<td>103 ± 20</td>
</tr>
<tr>
<td></td>
<td>Solvent</td>
<td>2.31 ± 0.48</td>
<td>95 ± 23</td>
<td>106 ± 18</td>
<td>100 ± 17</td>
<td>98 ± 20</td>
<td>91 ± 11</td>
</tr>
</tbody>
</table>

Values are mean ± SD. There are no significant differences between groups. E\textsubscript{max} = peak power output; G = curvature of the force-velocity hyperbola.

load only (data not shown) and R1 (table 1). Etanolone and its solvent did not modify \( -dF/dt \) (data not shown) and R2 (table 1).

Postrest recovery was studied after and during an isometric beating period. In control conditions, B1 was potentiated compared with B0, providing a ratio B1/B0 of 1.56 ± 0.12, which was not significantly different between groups and consistent with previous reports.\(^5\) Etanolone and its solvent did not significantly modify B0 (105 ± 16 and 107 ± 12% of control values, respectively at 10 µg \cdot ml\(^{-1}\)). As shown in figure 2, etanolone significantly decreased the ratio B1/B0 whereas its solvent alone did not.

The decay of mean active isometric force during the postrest recovery period is shown in figure 3. This decay fitted well to an exponential curve (0.93 < R < 0.99) and the control values of \( \tau \) (\( \tau = 3.8 ± 1.1 \) beats) were not significantly different between groups and were consistent with our previous studies.\(^5\) Even at 10 µg \cdot ml\(^{-1}\), etanolone in its solvent (4.5 ± 1.4 s; 3.8 ± 1.0 beats; difference not statistically significant) and its solvent alone (4.5 ± 1.2 s; 4.1 ± 1.2 beats; difference not statistically significant) did not significantly modify \( \tau \) (fig. 3).

Discussion

The effects of a drug on intrinsic myocardial contractility are difficult to assess in vivo because of limitations in the instruments used. We have previously investigated the effects of etanolone in its solvent (10 µg \cdot ml\(^{-1}\)) and in the solvent alone (\( n = 7 \)) on postrest recover time constant \( \tau \) (right) on the decay of mean active isometric force during the postrest recovery period. Data are expressed as the percentage (mean ± SD) of the force of the beat before rest (B0) and are plotted on a semilogarithmic scale. No significant differences in the recovery time constant \( \tau \) were observed.

Anesthesiology, V 83, No 4, Oct 1995

Changes in heart rate, preload, and afterload by the use of anesthetic agents that influence demand and central nervous system activity could have an important role in the effects of etanolone on cardiac function. The main result of our study is that etanolone did not induce a significant inotropic effect. Indeed, etanolone in 10 µg \cdot ml\(^{-1}\) did not modify Ymax and Y\textsubscript{n}.

Etanolone did not modify the heart rate or the systolic pressure. The results suggest that etanolone does not modify the contractility of the heart, and it may be useful as a myocardial relaxant.

The results of this study indicate that etanolone may be a useful agent for the treatment of myocardial ischemia.

Fig. 2. Effects of etanolone in its solvent (\( n = 8 \)) and those of its solvent alone (\( n = 7 \)) on the postrest potentiation. Data are expressed as B1/B0 ratio (mean ± SD), where B0 = the active isometric force of the beat before rest and B1 = the active isometric force of the first beat after rest. These data were obtained in isometrically contracting muscles. The \( P \) value refers to intergroup comparison; * \( P < 0.05 \) versus control.

Fig. 3. Effects of etanolone (10 µg \cdot ml\(^{-1}\)) in its solvent (\( n = 8 \)) (left) and those of its solvent alone (\( n = 7 \)) (right) on the decay of mean active isometric force during the postrest recovery period. Data are expressed as the percentage (mean ± SD) of the force of the beat before rest (B0) and are plotted on a semilogarithmic scale. No significant differences in the recovery time constant \( \tau \) were observed.

Anesthesiology, V 83, No 4, Oct 1995
EFFECTS OF ETLANOLONE ON RAT MYOCARDIUM

changes in heart rate, preload, and afterload, especially with anesthetic agents that are also known to decrease oxygen demand and central nervous system activity, and consequently cardiac output. Thus, we have studied the effects of etlanolone on the intrinsic contractility of isolated rat left ventricular papillary muscle. The main result of our study is that etlanolone did not induce a significant inotropic effect on rat myocardium.

Indeed, etlanolone to 10 μg·ml⁻¹ did not significantly modify Vmax and AF (table 1), which test the inotropic state under low and high loads, respectively. Etlanolone did not modify G (table 2). G has been shown to be linked to myotheatal economy and crosstriceptent kinetics: 1-10 the more curved the hyperbola (i.e., the higher the value of G), the higher the muscle efficiency. Moreover, the peak power output (Emax) remained unchanged after etlanolone as a consequence of the absence of change in Vmax, AF, and G (table 2). These results show that etlanolone did not significantly modify energetics of rat myocardium.

Etlanolone did not modify R1. Under isometric conditions, the amplitude of sarcomere shortening is twice that observed in isometric conditions, and the time course of isotonic relaxation occurs earlier and more rapidly that than of isometric relaxation, partly through two mechanisms: (1) the easier removal of calcium from troponin C, due to a decrease in myofilament calcium sensitivity, and (2) the rapid uptake of calcium by the SR. Under low load, SR appears to play a major role in the regulation of the time course of isotonic relaxation. Our results therefore suggest that etlanolone did not modify the uptake of calcium by the SR. This result contrasts with those previously reported with other intravenous anesthetic agents (propofol, 11 etomidate, 12 ketamine, 5 and chlorpromazine 13), which impair (at least at high concentrations) calcium uptake from the SR.

The characteristics of force postrest recovery in the rat ventricle have been extensively studied 1-10 and are shown in figure 3. B1 is more dependent on SR than subsequent beats and B0. This postrest potentiation is abolished by ryanodine, a specific inhibitor of SR function, which locks the calcium release channels of the terminal cisternae in the open state, 11 and therefore depends on the capacity to release calcium from the SR. The potentiated contraction B1 also depends on the capacity of SR to progressively load more and more calcium during the rest period and thus on the capacity of SR to reaccumulate large amounts of calcium. 11 In our study, etlanolone decreased B1 and the ratio B1/ B0 whereas its solvent did not (fig. 2). These results suggest that etlanolone impaired either SR calcium release function or the capacity of SR to load calcium during the rest period. The effects of etlanolone on SR functions contrast with those previously reported with propofol. 12 Indeed, propofol has been demonstrated to impair isotonic relaxation, suggesting that propofol decreases SR calcium uptake whereas etlanolone did not; and propofol has been shown not to modify postrest potentiation, suggesting that propofol does not modify SR calcium release, whereas etlanolone did after rest potentiation. However, the absence of negative inotropic effect (table 1) suggests that the effects of etlanolone on SR functions remained moderate.

The decay of force during the postrest recovery has been shown to be exponential, and τ has been assumed to represent the time required for the SR to reset itself and was therefore used to test some of the SR functions. 12,13 In our study, no significant changes in τ were observed with etlanolone and its solvent (fig. 3). These results suggest that etlanolone did not modify this SR function, in contrast with that previously noted with ketamine 5 but not propofol. 12

R2 was not modified by etlanolone. Under isometric conditions and because of the slight sarcomere shortening, myofilament calcium sensitivity is less decreased than in isometric conditions and becomes the limiting step that appears to play a major role in the regulation of the time course of isotonic relaxation. 11 The absence of any lusitropic effect of etlanolone under high load suggests that it did not modify myofilament calcium sensitivity. The following points must be considered in the assessment of the clinical relevance of our results. First, because this study was conducted in vitro, it dealt only with intrinsic myocardial contractility. Observed changes in cardiac function after in vivo etlanolone administration also depend on modifications in venous return, afterload, and reflex regulatory and compensatory mechanisms. Nevertheless, the lack of significant inotropic effect in vitro are consistent with the moderate cardiovascular effects of etlanolone in vivo. 1,8 Second, this study was conducted at 29°C at a low-stimulation frequency; however, papillary muscles must be studied at this temperature because stability of mechanical parameters is not sufficient at 37°C, and at a low frequency because high-stimulation frequency induces core hypoxia. 12 Third, it was performed on rat myocardium, which differs from human myocardium.
In rat myocardium, a negative staircase effect is observed (an increase in stimulation frequency decreases force), contractility is high, the calcium-induced calcium release from the SR is more highly developed than in other species, and myosin isoforms are predominantly of the fast VI type. These points may be important because opposing inotropic effects of anesthetic agents have been observed in different species.

Fourth, this study was conducted in normal animals. Indeed, the effects of anesthetic agents on intrinsic myocardial contractility may differ or not differ between normal and diseased myocardium. Furthermore, because etalolane is highly bound to plasma protein and because the bathing solution was protein-free, some of the concentrations tested might be considered as relatively high. Nevertheless, the wide range of concentrations tested were thought to encompass therapeutic concentration range.

In conclusion, in this study conducted on isolated rat left ventricular papillary muscle, etalolane did not modify intrinsic myocardial contractility. Moreover, etalolane induced no significant, lusitropic effects and did not modify energetic parameters. Etalolane decreased the postrest potentiation without significant changes in the postrest recovery time constant, suggesting that etalolane may decrease SR calcium release in extreme conditions. These results could be important because most anesthetic agents decrease myocardial contractility.

References
22. Fabrio A, Fabbio F: Calcium-induced release of calcium from the sarcoplasmic reticulum of skinned cells from adult human, dog, cat, rabbit, and frog hearts and from fetal and newborn rat ventricles. Ann N Y Acad Sci 507:491–522, 1995

Anesthesiology, V 83, No 4, Oct 1995