In Vitro Effects of Propofol on Rat Myocardium
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Propofol is a short-acting intravenous induction agent that induces cardiovascular depression. However, the effects of propofol on intrinsic myocardial contractility remain debatable. Thus, we studied the effects of three concentrations of propofol (1, 3, and 10 μg·mL⁻¹, respectively) and its solvent on the mechanics and energetics of isolated rat left ventricular papillary muscles. Propofol and its solvent did not induce any significant inotropic effect as shown by the lack of significant changes in maximum unloaded shortening velocity and in active isometric force. Nevertheless, propofol induced a slight decrease in isometric force (92 ± 6%, 95 ± 5%, and 95 ± 4%, respectively, all P < 0.01) under certain experimental conditions (i.e., after isometric stabilization). Using various afterloaded twitches, the peak power output and the curvature of the force-velocity curve were calculated. Propofol and its solvent did not significantly modify these two energetic parameters, indicating that it did not change myothermodynamic and cross-bridge kinetics. Propofol impaired isotonic relaxation, suggesting that it decreased calcium uptake by the sarcoplasmic reticulum, whereas its solvent alone did not. However, alteration of sarcoplasmic reticulum function was moderate, since posttrest potentiation and posttrest recovery were unmodified after propofol. It was concluded that propofol induces moderate changes on intrinsic myocardial contractility. These results suggest that cardiovascular depression observed with propofol in vitro is not related to intrinsic myocardial depression. (Key words: Anesthetics, intravenous: propofol. Heart, papillary muscle: contractility; relaxation.)

PROPOFOL is a new short-acting intravenous induction agent suitable for use as a total intravenous anesthetic agent. The acute cardiovascular changes following induction of anesthesia with propofol have been reported in patients with and without cardiac disease. In patients without cardiac disease, propofol induced a significant decrease in arterial blood pressure and total vascular resistance and a decrease in cardiac output, with no significant changes in heart rate. A similar degree of cardiovascular depression has been seen in patients with impaired left ventricular function or coronary artery disease. Propofol has been found to induce greater cardiovascular depression than that following thiopental or methohexital. The effect of propofol on intrinsic myocardial contractility remains debatable. Using gated radionuclide cineangiography, Lepage et al. reported no variation in global ejection fraction during induction of anesthesia with propofol in humans. In contrast, Mülner et al., using peak arterial blood pressure and end-systolic volume measured by means of transesophageal echocardiography, reported negative inotropic properties for propofol. In an open-chest pig model, Coetzee et al. found that propofol induced changes in the end-systolic pressure–length relationship, which also suggests a decrease in myocardial contractility. However, because of concomitant changes in preload, systemic resistance, baroreflex activity, and central nervous system activity, the precise effects of propofol on intrinsic myocardial contractility are difficult to assess in vitro.

Thus, we studied the effects of propofol on rat ventricular papillary muscle in vitro. The experimental model used in the present study enabled us to determine the effects of propofol on the mechanics and energetics of cardiac muscle. Because propofol is available in an emulsified media, we also studied the specific effects of this solvent on the intrinsic mechanical properties of rat cardiac papillary muscle.

Material and Methods

EXPERIMENTAL PROTOCOL

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.

After brief anesthesia with ether, the hearts were quickly removed from 17 adult male Wistar rats, weighing 400–510 g. Left ventricular papillary muscles (n = 29) were carefully excised and suspended vertically in a 60 ml Krebs-Henseleit bicarbonate buffer solution containing (millimolar) 118 NaCl, 4.7 KCl, 1.2 MgSO₄ ·7H₂O, 1.1 KH₂PO₄, 25 NaHCO₃, 2.5 CaCl₂ · 6H₂O, and 4.5 glucose. Preparations were field-stimulated at 0.12 Hz by two

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Accepted for publication December 13, 1991.

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platinum electrodes with rectangular wave pulses of 5-ms duration just above threshold. The bathing solution was bubbled with 95% O₂–5% CO₂, resulting in 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 (Lₘₐₓ), papillary muscles recovered their optimal mechanical performance, which remained stable for many hours. Suitable preparations were selected, as previously reported.¹⁵

Control values of each mechanical parameter were recorded. Then, the extracellular calcium concentration ([Ca²⁺]ₒ) was decreased from 2.5 to 0.5 mM. [Ca²⁺]ₒ was decreased for the following reasons: 1) because rat myocardial contractility is nearly maximum at 2.5 mM [Ca²⁺]ₒ,¹⁴ it is difficult to quantify a positive inotropic effect without previously decreasing [Ca²⁺]ₒ to 0.5 mM¹⁶,¹⁴; 2) in rat cardiac muscle, a postrest contraction study is more sensitive at a low [Ca²⁺]ₒ.¹⁵ Because propofol is insoluble in aqueous media, we tested the commercially available form of propofol in which a soya bean emulsion is the solvent (Diprivan®, ICI Pharma). Papillary muscles were divided into three groups. In the propofol group (n = 10), propofol in its solvent was added to the bathing solution. Concentrations of propofol during anesthesia range from 1 to 5 μg·ml⁻¹.¹⁶,¹⁷ Three concentrations of propofol were tested in a cumulative manner: 1 μg·ml⁻¹ (5.6 μM), 3 μg·ml⁻¹ (16.8 μM), and 10 μg·ml⁻¹ (56 μM), with 15 min elapsing between each dose. In the solvent group (n = 10), the solvent alone was tested at three concentrations corresponding to that obtained in the propofol group, in the same cumulative manner. In a third group (n = 9), propranolol 10⁻⁶ M (Avlocardyl® ICI Pharma) was added before the solvent alone was tested.

The electromagnetic lever system has been previously described.¹⁸ 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 obtained with a Hewlett-Packard 1000 computer, as previously described.¹⁹

MECHANICAL PARAMETERS

Conventional mechanical parameters at Lₘₐₓ were calculated from three twitches. The first twitch was isotonic 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 in order to slow the first and rapidly shortening overshoot resulting from the recoil of series passive elastic components, as previously reported¹⁹; the maximum unloaded shortening velocity (Vₘₐₓ) was determined from this twitch. The third twitch was fully isometric at Lₘₐₓ.

The mechanical parameters characterizing the contraction and relaxation phases, and the coupling between contraction and relaxation are defined as follows (fig. 1).

Contraction Phase

We determined Vₘₐₓ 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 (+dF · dt⁻¹). Vₘₐₓ and AF tested the inotropic state under low and high loads respectively.

Relaxation Phase

We determined maximum lengthening velocity of the twitch with preload only (maxVr) and the peak of the negative force derivative at Lₘₐₓ normalized per cross-sectional area (−dF · dt⁻¹). These two parameters tested the lusitropic state under low- and high-loading conditions, respectively. Since changes in the contraction phase induce coordinated changes in the relaxation phase, variations of contraction and relaxation must be simultaneously considered to quantify drug-induced changes in lusitropy. Indexes of contraction–relaxation coupling have therefore been developed.¹³,²⁰

Contraction–Relaxation Coupling

Coefficient R₁ = maxVc / maxVr, where maxVc = maximum shortening velocity of the twitch with preload.
only, tests the coupling between contraction and relaxation under low load. Under isometric conditions the amplitude of sarcomere shortening is twice that observed under isometric conditions. Due to the lower sensitivity of troponin C for calcium when cardiac muscle is markedly shortened under low load, relaxation proceeds more rapidly than contraction, apparently due to rapid uptake of calcium by the sarcoplasmic reticulum (SR). Thus, R1 (contraction–relaxation coupling under low load) is significantly less than 1 and tests SR function. Coefficient \( R_2 = \frac{(+dF\cdot dt^{-1})}{(-dF\cdot dt^{-1})} \) tests the coupling between contraction and relaxation under high load. When muscle is contracting isometrically, sarcomeres shorten little. Due to a higher sensitivity of cardiac muscle troponin for calcium, the time course of relaxation is determined by calcium unbinding from troponin C rather than by calcium sequestration by the SR. Thus, R2 (contraction–relaxation coupling under heavy load) is greater than 1 and reflects myofilament calcium sensitivity.

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

**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. The following energetic parameters were derived from the Hill’s hyperbola equation \( (\text{TF}/V) \text{ relationship} \); the peak power output \( (E_{\text{max}}) \) and curvature of the hyperbola (G). G has been shown to be linked to the myothermial economy and cross-bridge kinetics; the more curved Hill’s hyperbola \( (i.e., \text{the higher the value of G}) \), the higher the muscle efficiency. During cardiac hypertrophy, impaired myocardial performance is associated with an increase in G and higher myothermial economy.

**Postrest Contraction**

Recovery of a stable, reproducible isometric contraction after a rest interval was studied to identify the effects of propofol on both sources of myofibrillar activating calcium: sarcolemma and SR. During rest in the rat, SR accumulates calcium in addition to that accumulated with regular stimulation, and the first beat after the rest interval (B1) is more forceful than the last beat before the rest interval (B0). During the 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 a few beats. Therefore, the postrest potentiated contraction study may provide insight into a biochemically unaltered preparation concerning the effects of propofol on the SR function. AF during postrest recovery was studied after a 1-min rest. The rate constant \( \tau \) of the exponential decay of AF was determined as previously described. \( \tau \) was assumed to represent the time required for the SR to reset itself and therefore was used to test the SR function.

**Gas Analysis**

The solvent of propofol is an emulsified media that may modify the physical properties of the bathing solution. Indeed, after introduction of the solvent, the macroscopic aspect of oxygen bubbles in the Krebs-Henseleit solution was modified, suggesting an increase in surface tension, related to the presence of the emulsified media. Because this modification could modify papillary muscle oxygenation, which is critical in this model, we measured the \( \text{pH} \), partial pressures of oxygen \( (P_{\text{O}_2}) \) and carbon dioxide \( (P_{\text{CO}_2}) \), and bicarbonate concentrations in the Krebs-Henseleit solution \( (\text{pH}/\text{blood gas analyzer 1506, Instrumentation Laboratory, Milano, in control conditions and 15 min after the addition of propofol (10} \mu \text{g} \cdot \text{ml}^{-1}) \) in its solvent \((n = 8)\) or its solvent alone \((n = 8)\), at a corresponding concentration. Preliminary studies showed that a plateau was achieved within 5 min of bubbling with 95% \( \text{O}_2\)–5% \( \text{CO}_2\).

**Statistical Analysis**

Data are expressed as mean ± standard deviation. Comparison between groups was performed using repeated-measures analysis of variance and Newman-Keuls’ test, and the Student \( t \) test when appropriate (PCSMM software, Deltasoft, Meylan, France). The energetic parameters were derived from the Hill’s equation using multiple linear regression and the least squares method, as previously reported. The beat-to-beat decay of active isometric force during postrest recovery was plotted against the number of beats and fitted to an exponential curve, and regression was performed using the least squares method. Comparison of the slope of the regression curves was performed using Student’s \( t \) test. All comparisons were two-tailed, and a \( P \) value of less than 0.05 was required to reject the null hypothesis.

**Results**

Twenty nine papillary muscles were used in the present study. The mean cross-sectional area was 0.83 ± 0.09 mm\(^2\) (range 0.70–0.90), the mean \( L_{\text{max}} \) was 5.4 ± 2.7 mm (range 3.0–7.0), the mean ratio of resting force and iso-
metric TF was 0.11 ± 0.03 (range 0.06–0.16); at 2.5 mM [Ca$^{2+}$], contraction–relaxation coupling under low load (R1) was 0.74 ± 0.08 (range 0.61–0.85). These values indicated that papillary muscles did not suffer core hypoxia or careless excision. A decrease in contractility was observed as [Ca$^{2+}$] was decreased from 2.5 to 0.5 mM: the decreases in V$_{\text{max}}$ (65 ± 13% of the value at a [Ca$^{2+}$] of 2.5 mM) and AF (52 ± 14% of the value at a [Ca$^{2+}$] of 2.5 mM) were consistent with previous reports.13,20

Propofol in its solvent and its solvent alone induced a slight but significant decrease in the partial pressure of oxygen in the bathing solution (table 1). The P$_{\text{CO}_2}$ and bicarbonate concentration were not modified, whereas the pH of the bathing solution slightly increased (table 1).

Propofol and its solvent induced no significant inotropic effect, as shown by the absence of significant changes in V$_{\text{max}}$ and AF (table 2). Nevertheless, when papillary muscles were studied after isometric stabilization (during postrest recovery study), a slight decrease in active isometric force was noted after propofol (fig. 2). Propofol induced a decrease in maxVr and contraction–relaxation coupling under low load (R1) (table 2), whereas its solvent alone did not. In contrast, propofol did not alter isometric relaxation (−dF · dt$^{-1}$) and contraction–relaxation coupling under high load (R2) (table 2). The solvent alone induced a slight but significant decrease in contraction–relaxation coupling under high load (R2), related to an increase in −dF · dt$^{-1}$ without any changes in +dF · dt$^{-1}$. Previous addition of propranolol did not modify the effects of the solvent on contraction–relaxation coupling under low (R1) and high-load (R2) (fig 3).

The force–velocity relationship was not modified by propofol and its solvent, as shown by the nonsignificant changes in E$_{\text{max}}$ and in G of the hyperbola (table 3).

In control conditions, the first beat (B1) after rest interval was potentiated as compared to the beat before rest (B0) (B1/B0: 138 ± 19%). Propofol induced a slight decrease in the potentiated contraction B1 but to a similar extent as that observed with B0 (fig. 2). Consequently, the ratio B1/B0 was not significantly modified by propofol at 1 µg · ml$^{-1}$ (142 ± 21%), 3 µg · ml$^{-1}$ (134 ± 17%), and 10 µg · ml$^{-1}$ (152 ± 20%). The decay in the mean active isometric force during the postrest recovery period fitted well with an exponential decay (0.92 < R < 0.99), and the control value of the rate constant (τ; 4.0 ± 0.4 beats) was consistent with our previous study.13 τ was not significantly modified by propofol at 1 µg · ml$^{-1}$ (3.7 ± 0.4 beats), 3 µg · ml$^{-1}$ (3.3 ± 0.4 beats), and 10 µg · ml$^{-1}$ (4.2 ± 0.4 beats).

Discussion

Numerous studies indicate that propofol administration is associated with cardiovascular depression.5–7 However, the precise effects of propofol on myocardial contractility remain debatable. The effects of a drug on intrinsic myocardial contractility are difficult to assess in vivo because of changes in heart rate, preload, and afterload,12 especially with anesthetic agents known also to decrease oxygen demand and central nervous system activity, and consequently cardiac output. We have studied the effects of propofol on the intrinsic contractility of isolated rat cardiac papillary muscle. The main result of our study is that propofol did not induce a significant inotropic effect on rat myocardium.

Indeed, propofol did not modify V$_{\text{max}}$ and AF. However, when papillary muscles were allowed to contract isometrically during the postrest contraction study, propofol slightly decreased the maximum isometric force (fig. 2). Previous mechanical events influence the contractility of papillary muscle,28 and the isometric force developed after a period of isometric beating is slightly less than that developed after a period of isotonic beating.29 The precise mechanism of this observation is not completely understood, although it may be due partly to changes in SR calcium stores or myofilament sensitivity to calcium. Nevertheless, it must be pointed out that even after the isometric stabilization of papillary muscles, propofol induced only a moderate decrease in isometric force.

Although most authors agree that propofol induces cardiovascular depression that is probably more pro-

<table>
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<tr>
<th>TABLE 1. Effects of Propofol (10 µg · ml$^{-1}$) in Its Solvent and of Its Solvent Alone on Krebs-Henseleit Solution Gas Analysis</th>
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<tr>
<td><strong>n = 8</strong></td>
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<tr>
<td>pH</td>
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<tr>
<td>P$_{\text{O}_2}$ (mmHg)</td>
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<td>P$_{\text{CO}_2}$ (mmHg)</td>
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<td>HCO$_3$ (mM)</td>
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</tbody>
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Values are mean ± SD. P$_{\text{O}_2}$ = partial pressure in oxygen; P$_{\text{CO}_2}$ = partial pressure in carbon dioxide; HCO$_3$ = bicarbonate concentration.

* P < 0.05 versus control. No differences between groups in control conditions were significant.
PROPOFOL AND CARDIAC MUSCLE

TABLE 2. Comparison of the Effects of Propofol in its Solvent (n = 10) and of its Solvent Alone (n = 10) on the Intrinsic Mechanical Properties of Rat Papillary Muscle

<table>
<thead>
<tr>
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<th>Control (absolute values)</th>
<th>Concentrations of Propofol or Equivalent Concentrations of Solvent (percent of control)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>1 µg·ml⁻¹</td>
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<tr>
<td>Contraction</td>
<td></td>
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<tr>
<td>Vₘax (Lₘax·s⁻¹)</td>
<td>Propofol</td>
<td>2.58 ± 0.58</td>
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<tr>
<td></td>
<td>Solvent</td>
<td>2.29 ± 0.65</td>
</tr>
<tr>
<td>maxVc (Lₘax·s⁻¹)</td>
<td>Propofol</td>
<td>1.45 ± 0.34</td>
</tr>
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<td></td>
<td>Solvent</td>
<td>1.39 ± 0.33</td>
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<tr>
<td>AF (mN·mm⁻²)</td>
<td>Propofol</td>
<td>26.5 ± 9.5</td>
</tr>
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<td></td>
<td>Solvent</td>
<td>34.1 ± 11.0</td>
</tr>
<tr>
<td>+dF·dt⁻¹ (mN·s⁻¹·mm⁻²)</td>
<td>Propofol</td>
<td>312 ± 110</td>
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<td></td>
<td>Solvent</td>
<td>297 ± 90</td>
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<td>Relaxation</td>
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<td>maxVR (Lₘax·s⁻¹)</td>
<td>Propofol</td>
<td>1.89 ± 0.59</td>
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<td></td>
<td>Solvent</td>
<td>2.06 ± 0.67</td>
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<tr>
<td>−dF·dt⁻¹ (mN·s⁻¹·mm⁻²)</td>
<td>Propofol</td>
<td>173 ± 50</td>
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<td></td>
<td>Solvent</td>
<td>140 ± 27</td>
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<tr>
<td>Contraction–relaxation coupling</td>
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<tr>
<td>R1 (low load)</td>
<td>Propofol</td>
<td>0.79 ± 0.11</td>
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<tr>
<td></td>
<td>Solvent</td>
<td>0.70 ± 0.10</td>
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<tr>
<td>R2 (high load)</td>
<td>Propofol</td>
<td>1.78 ± 0.19†</td>
</tr>
<tr>
<td></td>
<td>Solvent</td>
<td>2.10 ± 0.34†</td>
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</tbody>
</table>

Values are mean ± SD. Vₘax = maximum unloaded shortening velocity; maxVc = maximum shortening velocity; AF = isometric active force normalized per cross-sectional area; +dF·dt⁻¹ = peak of the positive force derivative normalized per cross-sectional area; maxVR = maximum lengthening velocity; −dF·dt⁻¹ = peak of the negative force derivative normalized per cross-sectional area; R1 = maxVc/ maxVR; R2 = +dF·dt⁻¹/−dF·dt⁻¹.

* P < 0.05 versus control.
† P < 0.05 versus solvent.

nounced than that of thiopental, conflicting results have been obtained in vivo as to the effects of propofol on intrinsic myocardial contractility. Using needle force probes inserted into the myocardium, Brüssel et al.⁴⁰ reported a negative inotropic effect of propofol. However, in their experimental study, dogs were previously anesthetized with ketamine, nitrous oxide, and fentanyl and were acutely instrumented, and preload was assessed by means of right atrial and pulmonary capillary wedge pressure but not by measurements of ventricular volume. Coetzee et al.¹⁰ also reported a negative inotropic effect of propofol, but their study was conducted in an acute open-chest experimental model, and the end-systolic pressure–length relationship that was used to assess myocardial contractility is not really independent of loading conditions. However, Goodchild and Serrao³¹ showed that the

![Fig. 2. Effects of propofol on the active isometric force of the postrest potentiated contraction. B0 = the beat before rest; B1 = the first beat after rest. Data are mean ± SD. *P < 0.01 compared to control.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931332/)

![Fig. 3. Effects of propofol (10 µg·ml⁻¹) in its solvent, of the solvent alone, and of the solvent in the presence of propranolol, on contraction–relaxation coupling under low (R1) or high (R2) load. Data are mean percent from control values ± SD. *P < 0.05 compared to control.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931332/)
TABLE 3. Comparison of the Effects of Propofol in its Solvent (n = 10) and its Solvent Alone (n = 10) on Papillary Muscle Energetics

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<tbody>
<tr>
<td></td>
<td></td>
<td>1 µg·mL⁻¹</td>
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<tr>
<td>G</td>
<td></td>
<td>2.31 ± 0.61</td>
</tr>
<tr>
<td></td>
<td>Propofol</td>
<td>2.62 ± 1.03</td>
</tr>
<tr>
<td></td>
<td>Solvent</td>
<td>15.1 ± 6.2</td>
</tr>
<tr>
<td></td>
<td>Propofol</td>
<td>15.5 ± 5.6</td>
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<tr>
<td></td>
<td>Solvent</td>
<td>96 ± 8</td>
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</table>

Values are mean ± SD. No differences were significant.

propofol-induced cardiovascular depression can be corrected by fluid administration in order to maintain preload constant in dogs in which all cardiovascular reflexes have been abolished. Using a radionuclide approach in humans, Lepage et al.⁸ concluded that propofol did not alter left ventricular performance. Our study shows that the cardiovascular depression of propofol is not related to a decrease in intrinsic myocardial contractility as assessed by this model. Indeed, propofol also resets baroreflex control of heart rate¹¹ and appears to be a potent vasodilator both on arterial and venous vessels.³²,³³ Rouby et al.³³ recently studied the peripheral vascular effects of propofol in patients in whom an artificial heart had been implanted: propofol was a very potent vasodilator agent. All in all, these results suggest that the cardiovascular depression of propofol is related to vasodilation and not to intrinsic myocardial depression.

Propofol did not modify G of the force–velocity curve (table 3). G has been shown to be linked to myocardial economy and cross-bridge kinetics,²⁵,²⁶ the more curved the hyperbola (i.e., the higher the value of G), the larger the ratio g₂/g₁, where g₁ = the maximum value of rate constant for attachment and g₂ = the maximum values of rate constants of cross-bridge detachment, and consequently the higher the muscle efficiency. Our results indicate that propofol did not significantly modify muscle efficiency or cross-bridge kinetics. Moreover, IEₘₐₓ remained unchanged as a consequence of the absence of change in VMₚₓₓ, AF, and G (table 3). These results show that propofol did not significantly modify energetics of rat myocardium.

Propofol slowed isotonic relaxation as shown by the decrease in maxVR and contraction–relaxation coupling under low load (R1), whereas its solvent alone did not (table 2). Under isotonic conditions, the amplitude of sarcomere shortening is twice that observed in isometric conditions,²¹ and the time course of isotonic relaxation occurs earlier and more rapidly than that of isometric relaxation, partly through two mechanisms²²: 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, the SR appears to play a major role in the regulation of isotonic relaxation. Our results therefore suggest that propofol impaired the uptake of calcium by the SR, because it decreased maxVR and increased R1 (table 2).

This impairment is moderate because both AF and VMₚₓₓ were not significantly decreased (table 2). Propofol slightly decreased postrest potentiated contraction (B1) but to the same extent as contraction before rest (B0) (fig. 2). Because B1 is more highly dependent on SR stores than B0, it is unlikely that this decrease be related to a decrease in the amount of calcium released by the SR. This result suggests that propofol modified neither the amount of calcium stored during rest nor the release of calcium by the SR. No change was observed in τ, the rate constant of the exponential decay of isometric force after the postrest potentiation. Since τ has been assumed to represent the time required for the SR to reestablish its steady-state calcium release and reuptake, these results show that propofol did not alter all SR functions but altered only calcium uptake. This might also explain why the moderate impairment in SR function did not induce any significant negative inotropic effect. The findings that propofol slowed isotonic relaxation and did not modify postrest potentiation (both used to assess SR function) are not contradictory. maxVR is rather an index of the time course of calcium reuptake by the SR; B1 and τ are rather indices of quantitative calcium sequestration by the SR. Thus, the dissociation between maxVR and τ is not contradictory if stimulation frequency is not too high; this is the case at a stimulation frequency of 0.12 Hz, enabling a complete calcium reuptake by the SR despite its slowed speed. Indeed, it has been previously shown that isotonic relaxation is earlier modified than postrest potentiation by drugs that depress SR function, such as ketamine.¹³

The isometric relaxation (−dF·dt⁻¹) and contraction–relaxation coupling under high load (R2), which assessed the lusitropic status of papillary muscle, were not modified by propofol. Under isometric conditions and because of the slight sarcomere shortening, the myofilament calcium sensitivity is less decreased than in isotonic conditions and
becomes the limiting step that appears to play a major role in the regulation of the time course of isometric relaxation. The absence of any inotropic effect of propofol under high load suggests that it did not modify the myofilament calcium sensitivity. The solvent induced a slight but significant decrease in R2.

Several hypotheses might explain such a decrease in R2: 1) core hypoxia of papillary muscle; 2) release and/or inhibition of uptake of endogenous catecholamines; or 3) a direct effect of the solvent. The possibility of core hypoxia arose because the solvent modified the macroscopic aspect of oxygen bubbling in the Krebs solution, probably because of an increase in solution surface tension. Indeed, a statistically significant decrease in PO2 was noted (table 1), but this decrease must be considered as too small to have any consequences on papillary muscle.27 Moreover, hypoxia also induced both a negative inotropic effect and an increase in R1, which were not observed with the solvent. The possible role of endogenous catecholamines that are synthesized in the rat ventricle34 was evoked because catecholamines decrease R2.28 However, the effect of the solvent on contraction–relaxation coupling under high load (R2) was not modified by propranolol (fig. 3). Moreover, catecholamines also induced a positive inotropic effect, which was not observed with the solvent alone, and it has been suggested that endogenous catecholamines are no longer present in rat papillary muscle after a 1-h stabilization period in vitro, since reserpine does not induce any positive inotropic effect.36 Consequently, it is concluded that the solvent has a direct effect on R2, suggesting a slight decrease in myofilament calcium sensitivity, and that propofol alone either had an opposite effect (i.e., slightly increased myofilament calcium sensitivity) or blunted the effect of its solvent. However, the control values of R2 in the propofol and solvent groups were statistically different, requiring a cautious interpretation of the slight decrease in R2 in the solvent group.

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 following in vivo propofol administration also depend on the balance between among in venous return, reduction in afterload, and compensatory mechanisms. Therefore, it is not surprising that a decrease in left ventricular function has been observed in some studies, although propofol appears to induce no significant negative inotropic effect in vitro. 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.27 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); the calcium-induced calcium release from the SR is more highly developed than in other species; and finally, the myosin isoforms are predominantly of the V1 type. Nevertheless, a species difference is probably not a major concern in the present study: Baron et al.37 recently showed that propofol does not induce a negative inotropic effect on rabbit myocardium (in an in vitro study of Langendorf preparation with blood circuit), which is closer to human myocardium. Fourth, this study was conducted in normal animals. Because Diedericks et al.38 have observed that propofol may induce irreversible failure in dogs with heart failure, an understanding of the effects of propofol on diseased myocardium requires further studies. Indeed, the effects of anesthetic agents on intrinsic myocardial contractility may differ between normal and diseased myocardium.39

In conclusion, in studies conducted on isolated rat papillary muscle, propofol induced moderate changes on intrinsic myocardial contractility: it produced no significant inotropic effect and a decrease in isotonic relaxation probably due to a slight decrease in calcium uptake by the SR. Cardiovascular depression observed with propofol in vitro is probably not related to intrinsic myocardial depression.

References