Mechanical and electrophysiological effects of thiopental on rat cardiac left ventricular papillary muscle

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Thiopental induces a negative inotropic effect on mammalian heart muscle, where it decreases Ca²⁺ current and Ca²⁺ release from the sarcoplasmic reticulum and reduces K⁺ currents. We analysed the effects of thiopental on the mechanical and electrical activities of rat myocardium, which differ markedly from those of other mammals. The effects of thiopental on mechanical parameters and on the transmembrane resting (RP) and action (AP) potentials of rat left ventricular papillary muscle were investigated. These effects were also studied in the presence of atenolol, a β-blocking agent, and 4-aminopyridine (4-AP), a blocker of the transient outward K⁺ current. Thiopental (3.8×10⁻⁶, 3.8×10⁻⁵ and 1.1×10⁻⁴ M) induced a dose-dependent positive inotropic effect. This positive inotropic effect persisted in the presence of atenolol (1×10⁻⁶ M) but did not develop in the presence of 1 mM 4-AP; 4-AP had a positive inotropic effect but not in the presence of thiopental. Moreover, thiopental (3.8×10⁻⁵ M) lengthened the plateau and the slow repolarizing phase of the AP, while 1 mM 4-AP only prolonged the plateau duration. In rat myocardium, the positive inotropic effect of thiopental in part mimics that of 4-AP, and in part may be explained by the lengthening of the slow repolarizing phase of the AP.

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Thiopental, one of the drugs most commonly used for general anaesthesia, generally induces a depressive effect on the human cardiovascular system.¹ It has a direct negative inotropic effect on a wide variety of heart preparations, including dog,² rabbit,³ ⁴ guinea pig,⁵ ⁶ ferret¹ and human atrial tissue.⁸ Thiopental decreases the Ca²⁺ current in dog² and guinea-pig heart muscle. It also reduces the delayed outward K⁺ current in guinea pig and rabbit⁶ ⁹ and frog heart muscle.⁷ In rabbit heart muscle, thiopental reduces Ca²⁺ release from the sarcoplasmic reticulum (SR) and inhibits ryanodine-induced Ca²⁺ release from the SR⁴ but does not alter Ca²⁺ uptake by the SR.¹⁰ The direct negative inotropic effect of thiopental on ferret papillary muscle results from decreased intracellular Ca²⁺ availability and, at least in part, from inhibition of trans-sarcolemmal Ca²⁺ influx, despite a slight increase in myofibrillar sensitivity to Ca²⁺.⁷

Numerous cellular processes regulating the homeostasis of contractile performance in rat myocardium differ from those observed in other species. Thus, in rat, Ca²⁺-induced Ca²⁺-release from the SR is more strongly developed than in other species.¹¹ In mammalian species, SR Ca²⁺-ATPase activity is more prominent than Na⁺/Ca²⁺ exchanger activity, but in the rat this dominance is much more marked (13-fold vs 2.5-fold).¹² Myosin ATPase activity and the percentage of the rapid V1 myosin isoform are higher in rat than in guinea-pig myocardium.¹³ The plateau duration of the action potential (AP) in the rat is extremely short compared with that in the guinea pig¹⁴ and most other mammals, including humans. Moreover, changes in AP duration and in the magnitude of contraction occurring during variations in heart rate are opposite in rat and in guinea pig.¹⁴ Because of the special characteristics of rat heart muscle, as well as the various species-related effects of thiopental, the direction of the inotropic effect of thiopental on rat myocardium cannot be predicted. The aims of the present study were to test the effects of thiopental on
contractile and electrical activities in rat cardiac left ventricular (LV) papillary muscle and to address the cellular mechanisms that might be involved in the positive inotropic effect induced by thiopental in rat myocardium.

**Materials and methods**

LV papillary muscles from adult Wistar rats (weighing 300–350 g) were used. Care of the animals conformed to the Helsinki Declaration, and the study was performed in accordance with the relevant French Ministry of Agriculture regulations.

**Mechanical study**

The heart was removed rapidly under ether anaesthesia. LV papillary muscles were carefully excised and suspended vertically in 40 ml of Krebs–Henseleit solution containing (in mM) 118 NaCl, 4.7 KCl, 1.2 MgSO₄, 1.1 KH₂PO₄, 25 NaHCO₃, 2.5 CaCl₂, 4.5 glucose, bubbled with 95% oxygen/5% carbon dioxide (pH 7.4) and maintained at 29°C. The preparations were field-stimulated at 0.12 Hz by two platinum electrodes with rectangular wave pulses (5 ms duration) just above threshold. After a 1 h stabilization period at Lmax (the initial muscle length at the apex of the length-active isometric tension curve), papillary muscles recovered their optimal performance. Suitable preparations were selected on the basis of the following criteria: (i) well individualized cylindrical shape, with cross-sectional area not exceeding 1.3 mm² and length at Lmax of >3.5 mm, (ii) ratio of resting force to total isometric force <0.25 and (iii) ratio of maximum shortening and lengthening velocities <0.85 at load equal to preload at Lmax. Adherent or bifid muscles were excluded from the study.

The electromagnetic lever system used to record mechanical data has been described elsewhere. Signals of force and length were recorded and digitized; the sampling rate was 1 kHz. All analyses were performed on the basis of digital data without filtering. Mechanical parameters characterizing the contraction phase (inotropic state) were calculated from three twitches with different levels of preload and afterload (Figure 1). The first twitch was isotonic and was loaded with preload only. The second twitch was loaded with preload then abruptly clamped to zero-load immediately after the electrical stimulus, using the zero-load clamp technique. The muscle was released from preload to zero load with critical damping in order to slow the first rapid shortening overshoot resulting from the recoil of the series passive elastic component. This technique allows measurement of the maximum shortening velocity of the unloaded muscle, which is a good parameter of inotropy. The following contraction parameters (Figure 1) were studied: maximum unloaded shortening velocity (Vmax, in Lmax s⁻¹), determined by the zero-load clamp technique (twitch 2); maximum extent of muscle shortening of the twitch with preload only (ΔL, as a percentage of Lmax) (twitch 1); peak isometric active force normalized per cross-sectional area (AF, in mN mm⁻²); positive peak of the force derivative normalized per cross-sectional area of the fully isometric twitch (+DF, in mN s⁻¹ mm⁻²); time to peak force of the isometric twitch (TPF, in ms) of the isometric twitch (twitch 3); and time to peak shortening (TPS, in ms) of the isometric twitch with preload only (twitch 1).

Control values of each mechanical parameter were first recorded using each muscle as its own control. Thiopental sodium (Specia) was added to the bath solution at three concentrations: 3.8×10⁻⁶ M (1 mg litre⁻¹) in group 1 (n=9); 3.8×10⁻⁵ M (10 mg litre⁻¹) in group 2 (n=13) and 1.1×10⁻⁴ M (30 mg litre⁻¹) in group 3 (n=9). Taking into account the protein binding of thiopental in blood, the concentration of
3.8×10⁻⁵ M corresponds to the free drug concentration, reached immediately after a bolus intravenous injection of 6 mg kg⁻¹ in humans.¹⁷ This concentration is higher than the concentration compatible with tracheal intubation in the rat.¹⁸ In group 4 (n=15), the effect of 3.8×10⁻⁵ M thiopental was studied after adding 1×10⁻⁶ M atenolol (Zeneca Pharma), a selective β₁ adrenergic antagonist. In group 5 (n=9), 3.8×10⁻⁵ M thiopental was tested after adding 1 mM 4-aminopyridine (4-AP, Merck) to inhibit the transient outward K⁺ current (Iₒ). In group 6 (n=9), 1 mM 4-AP was applied after treatment with 3.8×10⁻⁵ M thiopental. Changes in mechanical parameters were studied 30 min after adding atenolol and 4-AP and 45 min after adding thiopental.

Electrophysiological study
LV papillary muscles were pinned to the bottom of the tissue chamber maintained at 29°C and superfused with Krebs–Henseleit solution at a rate of 15 ml min⁻¹. Muscles were electrically stimulated, at a frequency of 0.2 Hz, by means of square pulses (5 ms duration) delivered through bipolar earth-isolated platinum electrodes, using an opto-electric coupling device. Transmembrane resting (RP) and action (AP) potentials were recorded with conventional glass microelectrodes (resistance 25–30 MΩ; tip potential less than ±3 mV) filled with 3 M KCl and connected to a differential voltage follower via Ag–AgCl platinum black electrodes (20). Stimulated AP were recorded in Krebs–Henseleit control solution after a stabilization period of 30 min before and 10 min after the addition of thiopental (3.8×10⁻⁶ M) and (3.8×10⁻⁵ M), 1 mM 4-AP or both.

The following AP parameters were measured: resting membrane potential (RP, in mV), overshoot (in mV), duration of the plateau (APDₒ, in ms) measured at 0 mV, and duration of the slow repolarizing phase of the AP (APDₐ, in ms) measured at +10 mV from the RP. In the figures, m corresponds to the number of impalements recorded from n muscles tested. Transmembrane potentials were displayed on a Nicolet 310 oscilloscope, digitized with a sampling rate of 1 kHz without filtering via a Labmaster acquisition card (DMA 100 OEM) driven by the software program Acquis1, linked to the mass storage of a personal computer.

Table 1 Inotropic parameters of left ventricular rat papillary muscles measured in Krebs–Henseleit solution (control) before and 45 min after the addition of each thiopental concentration. Values are mean (SD). Statistical significance of Student’s t-test for each mean of thiopental group compared with mean of control group: *P<0.05, **P<0.001

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (n=9)</th>
<th>Group 2 (n=13)</th>
<th>Group 3 (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Thiopental 3.8×10⁻⁵ M</td>
<td>Thiopental 3.8×10⁻⁴ M</td>
</tr>
<tr>
<td>Vₘₐₓ (Lₘₐₓ s⁻¹)</td>
<td>4.1 (0.9)</td>
<td>4.5 (0.9) **</td>
<td>4.4 (0.8)</td>
</tr>
<tr>
<td>ΔL (% Lₘₐₓ)</td>
<td>20 (3)</td>
<td>21 (3) **</td>
<td>23 (4)</td>
</tr>
<tr>
<td>AF (mN mm⁻²)</td>
<td>55 (12)</td>
<td>58 (11) **</td>
<td>55 (13)</td>
</tr>
<tr>
<td>+DF (mN mm⁻¹ s⁻¹)</td>
<td>638 (151)</td>
<td>693 (164) **</td>
<td>668 (165)</td>
</tr>
<tr>
<td>TPS (ms)</td>
<td>164 (8)</td>
<td>153 (6) **</td>
<td>160 (10)</td>
</tr>
<tr>
<td>TPF (ms)</td>
<td>162 (14)</td>
<td>149 (8) **</td>
<td>151 (12)</td>
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Results
The addition of 3.8×10⁻⁵ M thiopental to the control solution induced a positive inotropic effect which reached a maximum steady-state value within 30 min, as shown in Figure 2. Table 1 summarizes the effect of increasing thiopental concentrations from 3.8×10⁻⁶ M to 1.1×10⁻⁴ M on the inotropic parameters. Thiopental significantly increased Vₘₐₓ, AF, +DF and ΔL, and shortened TPF and TPS. Only AF was unaffected by 1.1×10⁻⁴ M thiopental.

A significant increase in Vₘₐₓ, AF, +DF and ΔL occurred when thiopental (3.8×10⁻⁵ M) was applied to muscles...
Table 2 Inotropic parameters of left ventricular rat papillary muscles in group 4 (n=15) measured in Krebs–Henseleit solution containing the blocker atenolol (1×10⁻⁶ M) applied 1 h before addition of 3.8×10⁻⁵ M thiopental (for 45 min). Values are mean (SD). n, Number of muscles tested. Student’s t-test for paired data: **P<0.001 for atenolol + thiopental compared with atenolol

<table>
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<th>Atenolol + thiopental</th>
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<tbody>
<tr>
<td>Vₘ₅ (lₘ₅ s⁻¹)</td>
<td>4.7 (1.2)</td>
<td>5.0 (1.3)**</td>
</tr>
<tr>
<td>ΔL (% lₘ₅)</td>
<td>25 (6)</td>
<td>27 (6)**</td>
</tr>
<tr>
<td>AF (mN mm⁻²)</td>
<td>51 (14)</td>
<td>54 (17)**</td>
</tr>
<tr>
<td>+DF (mN s⁻¹ mm⁻²)</td>
<td>608 (189)</td>
<td>665 (224)**</td>
</tr>
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</table>

Previously treated with 1×10⁻⁶ M atenolol (Table 2). A positive inotropic effect was observed when 1 mM 4-AP was added to the Krebs–Henseleit solution. As shown in Table 3, 4-AP significantly increased Vₘ₅. AF and +DF. Addition of thiopental (3.8×10⁻⁵ M) to a solution containing 4-AP failed to change the inotropic effect further, except for a slight (3%) but significant reduction in +DF (Table 3). Table 4 shows that addition of 4-AP to the solution containing 3.8×10⁻⁵ M thiopental had no effect on the inotropic parameters.

The addition of 3.8×10⁻⁵ M thiopental (Figure 3a and b) to the Krebs–Henseleit solution did not change the resting membrane potential or amplitude of the AP overshoot. In contrast, it lengthened the plateau (APD₀) and the slow final repolarization phase of AP (APD₁₀). The effects of 3.8×10⁻⁵ M and 3.8×10⁻⁵ M thiopental on the AP are summarized in Figure 3b; 3.8×10⁻⁶ M thiopental significantly lengthened APD₁₀, while 3.8×10⁻⁵ M thiopental lengthened both APD₀ and APD₁₀. The addition of 1 mM 4-AP to the control solution lengthened APD₀ but did not change RP or APD₁₀ (Figure 4a). Further addition of thiopental (3.8×10⁻⁵ M) to the solution containing 4-AP (Figure 4a) markedly increased APD₁₀, but did not change the other AP parameters. Figure 4b summarizes the effects of 4-AP alone on AP parameters and those established with further addition of thiopental (3.8×10⁻⁵ M) to the solution containing 4-AP.

Discussion
We examined the effects of thiopental at concentrations corresponding to plasma concentrations achieved during human¹⁷ and rat¹⁸ anaesthesia on the mechanical parameters and transmembrane potentials of rat cardiac papillary muscle. The main results were that (i) thiopental induced a positive inotropic effect and lengthened PA duration; (ii) it produced a positive inotropic effect on atenolol-pretreated muscles; and (iii) addition of thiopental to a solution containing 4-AP did not lead to any further increase in inotropy and addition of 4-AP to a solution containing thiopental did not increase inotropy. The positive inotropic response of rat heart muscle to thiopental reported in the present study differed markedly from that observed in other species— in which the drug causes a dose-dependent depression of contraction. In species other than rat, this negative inotropic effect may be due to an inhibitory effect of thiopental on the Ca²⁺ influx occurring via voltage-dependent Ca²⁺ channels, as suggested by the reduction of slow-channel-mediated action potentials in the dog, the decline in the aequorin signal in ferret papillary muscle and the reduction in the Ca²⁺ current in guinea-pig ventricular myocytes. This negative inotropic response has also been attributed to an effect of thiopental on the SR. Thus, in rabbit heart muscle, thiopental reduces Ca²⁺ release from the SR and inhibits ryanodine-induced Ca²⁺ release from the SR. To lead to a durable negative inotropic effect, however, the reduction in SR release must be accompanied by an alteration in uptake, causing a decrease in inotropy. However, it has been shown that in the rabbit, thiopental does not alter Ca²⁺ uptake by the SR. Moreover, some effects of thiopental are expected to generate a positive inotropic response, such as an increase in myofibrillar sensitivity to Ca²⁺ and an increase in the duration of the AP. This lengthening of AP duration has been observed in dog papillary muscle, in ventricular myocardium of rabbit and frog and in ventricular myocytes of guinea pig and has been attributed to a reduction of K⁺ conductances contributing to the repolarization of the cardiac AP. In frog atrial myocytes, thiopental depresses resting K⁺ currents by attenuating the rectifying inward K⁺ (Iₖ1) and delayed outward K⁺ currents. In guinea-pig and rabbit isolated ventricular myocytes, thiopental prolongs the repolarization of the AP, depresses the inward and outward

Table 3 Inotropic parameters of left ventricular rat papillary muscles in group 5 (n=9), measured in Krebs–Henseleit solution (control) before and after the addition of 1 mM 4-AP (for 30 min) then 3.8×10⁻⁵ M thiopental (for 45 min). Values are mean (SD). n, Number of muscles tested. Student’s t-test for paired data with Bonferroni correction: *P<0.05 and **P<0.001 for 4-AP compared with control; †P<0.05 for 4-AP + thiopental compared with 4-AP

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Thiopental</th>
<th>Thiopental + 4-AP</th>
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<tbody>
<tr>
<td>Vₘ₅ (lₘ₅ s⁻¹)</td>
<td>5.6 (0.9)</td>
<td>6.2 (1.2)**</td>
<td>5.9 (1.0)</td>
</tr>
<tr>
<td>ΔL (% lₘ₅)</td>
<td>24 (3)</td>
<td>26 (3)**</td>
<td>26 (3)</td>
</tr>
<tr>
<td>AF (mN mm⁻²)</td>
<td>63 (14)</td>
<td>71 (14)*</td>
<td>74 (15)</td>
</tr>
<tr>
<td>+DF (mN s⁻¹ mm⁻²)</td>
<td>737 (172)</td>
<td>887 (195)**</td>
<td>927 (236)</td>
</tr>
</tbody>
</table>
components of the inward rectifier K$^+$ current and inhibits the delayed rectifier K$^+$ current. Thiopental has also been reported to reduce $I_{k1}$ in rat and human ventricular myocytes. It is generally accepted that lengthening of the cardiac AP increases the availability of intracellular Ca$^{2+}$ and produces a positive inotropic effect. Moreover, thiopental induces a slight increase in myofibrillar sensitivity to Ca$^{2+}$ which may help produce a positive inotropic effect on myocardium. The ability of thiopental to prolong the AP conflicts with its negative inotropic effect induced in

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**Fig 3** Effect of thiopental on the action potential (AP) of rat LV papillary muscle recorded in Krebs–Henseleit control solution at a frequency of 0.2 Hz, using intracellular microelectrodes. (A) AP traces recorded on the same papillary muscle. (B) Histogram showing the effect of 3.8×10$^{-6}$ M and 3.8×10$^{-5}$ M thiopental on the AP parameters. Mean±SD of $m$ impalpements recorded from $n$ muscles. Control: $m=20$, $n=8$; thiopental 3.8×10$^{-6}$ M: $m=12$, $n=4$; thiopental 3.8×10$^{-5}$ M: $m=16$, $n=6$. Student’s $t$-test for paired data: *$P<0.05$. RP, resting membrane potential; OS, overshoot; APD$_0$, duration of the plateau measured at 0 mV; APD$_{10}$, duration of the slow repolarizing phase of the AP measured at a membrane potential +10 mV higher than RP.

**Fig 4** Effect of 1 mM 4-aminopyridine (4-AP) and 3.8×10$^{-5}$ M thiopental on the action potential (AP) of rat papillary muscle recorded in Krebs–Henseleit solution, at a frequency of 0.2 Hz, using intracellular microelectrodes. (A) Top: dashed line, control solution; solid line, 4-AP; bottom: dashed line, 4-AP; solid line, control solution containing 4-AP and thiopental. (B) Histogram showing the effect of successive addition of 4-AP and thiopental in the control solution (empty bar) on the AP parameters. Mean±SD of $m$ impalpements recorded from $n$ muscles. Control: $m=20$, $n=8$; 4-AP: $m=31$, $n=4$; 4-AP + thiopental 3.8×10$^{-5}$ M: $m=30$, $n=4$. Student’s $t$-test for paired data: *$P<0.05$. RP, resting membrane potential; OS, overshoot; APD$_0$, duration of the plateau measured at 0 mV; APD$_{10}$, duration of the slow repolarizing phase of the AP measured at a membrane potential +10 mV higher than RP.
most species. The direction of change in inotropy after thiopental treatment in cardiac muscle is partly determined by the overall resultant of the different and opposed effects of thiopental on (i) transsarcolemmal Ca\(^{2+}\) and K\(^+\) currents, (ii) Ca\(^{2+}\) movement through the SR membrane and (iii) myofibrillar sensitivity to Ca\(^{2+}\). In most species, this resultant effect is negative, except in our study where it was shown to be positive in the rat. However, this effect is certainly dose dependent and it has been shown that the percentage of cell shortening in rat ventricular myocytes is significantly altered at a thiopental concentration of >1×10\(^{-4}\) M. The observation in our study that the inotropic effect of thiopental was still present when β-receptors were blocked by atenolol suggested that this effect of thiopental on the inotropy of rat papillary muscle cannot be attributed to an agonist effect of the anaesthetic on β adrenoceptors, but involves a mechanism different from activation of the cAMP cascade.

Rat cardiac AP consists of a spike induced by the fast inward Na\(^+\) current, followed by a short plateau generated by the inward Ca\(^{2+}\) current, which is modulated by the transient outward K\(^+\) current (I\(_{\text{o transient}}\)), and a slow repolarization phase thought to be due to the development of the delayed outward K\(^+\) current and the electrogenic (3 Na\(^+\)/1 Ca\(^{2+}\)) of the Na\(^+\)/Ca\(^{2+}\) exchanger. The importance of I\(_{\text{o transient}}\) in determining early repolarization during the plateau has been shown in normal and pathological mammalian cardiac muscles. Inhibition of I\(_{\text{o transient}}\) by 4-AP in rat heart muscle increases the duration of the AP plateau.

In our study, the lengthening of the plateau induced by thiopental suggests that the anaesthetic exerts a 4-AP-like effect. Lengthening of the AP of rat cardiac ventricular myocytes, after application of a control solution containing 4-AP, leads to a more sustained Ca\(^{2+}\) current associated with an increased contractile response. 4-AP had a marked positive inotropic effect on rat left ventricular papillary muscle. Thus, the extended plateau induced by thiopental which occurred in a range of membrane potentials within which a large proportion of Ca\(^{2+}\) channels remains activated, may partly account for the increase in contractile force.

Thiopental also lengthened the slow repolarizing phase of the AP. This lengthening occurred in the presence or absence of 4-AP and may be a result of a decrease in both the delayed outward K\(^+\) current and I\(_{\text{Ca transient}}\). Lengthening of AP duration has been associated with an increase of inotropy because greater Ca\(^{2+}\) influx is expected during this period. Given that, in rat myocardium, Ca\(^{2+}\)-induced Ca\(^{2+}\) release from the SR is highly sensitive to Ca\(^{2+}\) influx into the cells, greater Ca\(^{2+}\) influx during the AP may contribute to increased Ca\(^{2+}\) release from the SR and thus to a positive inotropic effect. Such a mechanism is suggested to explain the positive inotropic effect of an α1-adrenergic agent and of the immunosuppressant agent FK 506. However, to maintain a positive effect on the systolic Ca\(^{2+}\) transient, a drug may also modify processes other than Ca\(^{2+}\)-induced Ca\(^{2+}\) release. For example, in the case of FK 506 it has been suggested that the sustained positive inotropic effect could be due to inhibition of the Na\(^+\)/Ca\(^{2+}\) exchange, resulting in an increase in Ca\(^{2+}\) availability for SR uptake. In the case of thiopental, further studies are necessary to investigate such a mechanism.

One of the limitations of our study is the use of a low stimulation frequency. In the rat, a low stimulation frequency induces an increase in inotropy because a prolonged diastole leads to an increase in SR Ca\(^{2+}\) uptake. Each contraction takes place after an 8 s diastolic pause, allowing a return to baseline diastolic Ca\(^{2+}\) level, thus, a drug-induced anomaly of this uptake can be hidden. However, most mechanical studies use such a low frequency to avoid the many rhythm anomalies induced by high frequencies. Moreover, it has been shown that thiopental does not alter SR uptake, at least in the rabbit.

In conclusion, this study shows that thiopental increases inotropy in rat cardiac papillary muscle. This positive inotropic effect can be linked to the lengthening of both the plateau and the slow repolarizing phase of the AP. This leads to an increase in the Ca\(^{2+}\) influx into the cardiac cells, which improves mechanical performance.

Acknowledgements
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