

Effects of Potassium Channel Blockers on Changes in Refractoriness of Atrial Cardiomyocytes Induced by Stretch

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Shortening of the effective refractory period (ERP) is regarded as one of the key mechanisms of atrial fibrillation (AF). Stretch is an important predisposing factor in the pathogenesis of AF. However, effective methods to counteract alteration of ERP induced by stretch still need to be explored. Although potassium channels play important roles in cardiac repolarization and refractoriness, the effects of potassium channel blockers on the alteration of repolarization and refractoriness induced by stretch are still unknown. Action potential duration (APD) and ERP were recorded using the standard intracellular microelectrode technique in the left atrial appendage cardiomyocytes of guinea pigs. Stretch accelerated repolarization of atrial cardiomyocytes and also shortened the ERP ($P < 0.05$). Dofetilide, a rapid delayed rectifying potassium ion channel (I_{Kr}) blocker; 4-AP, a transient outward potassium ion channel (I_{to}) blocker; and

BaCl₂, an inward rectifying potassium ion channel (I_{K1}) blocker could counteract the shortening of APD and ERP ($P < 0.01$). Glibenclamide, an ATP-sensitive potassium ion channel (I_{KATP}) blocker; 293-B, a slow delayed rectifying potassium channel (I_{Ks}) blocker; and DPO-1, an ultra-rapid delayed rectifying potassium ion channel (I_{Kur}) blocker all had no effect on APD and ERP ($P > 0.05$). Stretch could accelerate repolarization of atrial cardiomyocytes and shorten their ERP, and the I_{to} , I_{Kr} , and I_{K1} blockers could counteract the effects of stretch. *Exp Biol Med* 234:779–784, 2009

Key words: atrial fibrillation; potassium channel; repolarization; refractoriness; stretch

Introduction

Atrial fibrillation (AF) is a ubiquitous yet diverse cardiac arrhythmia with an overall prevalence close to 1% (1). Present therapeutic approaches to AF have failed to have a dramatic impact on AF. Moreover, all therapeutics have significant adverse effects (2, 3). AF's high prevalence and its associated risks, such as stroke (4) and mortality (5), have increased the need for better and more reliable therapeutic treatments (1).

Effective refractory period (ERP) shortening is regarded as one of the key mechanisms of AF (3, 6). Stretch is an important predisposing factor in the pathogenesis of AF (7, 8). AF can frequently be observed in those conditions that result in left or right atrial enlargement, for instance, during mitral valve stenosis and congestive cardiac failure (9, 10). However, effective methods to counteract the ERP alteration induced by stretch still need to be explored (3, 11).

Potassium channels play important roles in cardiac repolarization and refractoriness (11–13). In the present

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Table 1. The Electrophysiological Changes of Atrial Cardiomyocytes Induced by Stretch ($n = 20$)

Muscle length	RMP (mV)	APA (mV)	APD20 (ms)	APD50 (ms)	APD90 (ms)	ERP (ms)
Original	-71.3 ± 1.0	95.5 ± 2.3	37.9 ± 1.7	70.4 ± 1.7	128.8 ± 1.7	132.6 ± 1.8
110%	-72.3 ± 0.5	95.8 ± 2.2	33.6 ± 1.4^a	66.5 ± 1.6	125.4 ± 1.9	129.7 ± 1.6
120%	-71.3 ± 1.3	95.5 ± 2.4	27.3 ± 1.0^{ab}	55.3 ± 1.6^{ab}	117.8 ± 1.6^{ab}	118.9 ± 1.6^{ab}
Release	-71.5 ± 0.9	95.8 ± 1.9	36.7 ± 1.4	69.3 ± 0.9	127.4 ± 1.6	131.2 ± 1.4

^a $P < 0.05$.

^b $P < 0.01$ vs. 110% original length.

RMP, resting membrane potential; APA, action potential amplitude; APD20, action potential duration at 20%; APD50, action potential duration at 50%; APD90, action potential duration at 90%; ERP, effective refractory period.

study, we used an in vitro stretch model for atrial cardiomyocytes of guinea pigs to provide insight to the stretch-induced AF mechanisms and to the effects of potassium channel blockers on the alteration of repolarization and refractoriness induced by stretch.

Materials and Methods

Experimental Preparation. All procedures for animals were approved by the Animal Ethics and Experimentation Committee of the Tongji University, Shanghai, P.R. China, and were performed in accordance with the *Guide for the Care and Use of Laboratory Animals* published by the National Institutes of Health (NIH), U. S. A. (Publication No 85-23, revised 1996).

Male guinea pigs weighing 250–300 g were killed by cervical dislocation, and their hearts were quickly removed and placed in oxygenated (95% O₂, 5% CO₂) cold Tyrode's solution (mM) (NaCl 145, KCl 4.5, CaCl₂ 2.5, MgCl₂ 1.0, HEPES 20, glucose 11.1, pH 7.35, 95% O₂, 5% CO₂). The left atrial appendages (LAA) were isolated within 3 min. Mechanical stretch was applied directly using a cardiac stretch device under a stereoscopic microscope. The extent of stretch was expressed as the percentage change in cell length (L) relative to the original length: $\Delta L = (L_{\text{stretch}} - L_{\text{original}}) / L_{\text{original}} \times 100$.

Repolarization and Refractoriness Measurement. Standard intracellular microelectrode recording techniques were used. The voltage signal was amplified using the D.C. pre-amplifier and head-stage (NL102, Digitimer Ltd, Welwyn Garden City, U.K.), and data were analyzed by the PowerLab/8SP data acquisition system (Chart software, version 5.0, AD Instruments, Colorado Springs, CO). All samples were stimulated at 1 Hz with square-wave pulses of 1 ms in duration and double the threshold in amplitude. Glass capillary microelectrodes, filled with 3 M KCl, with a tip resistance of 10–20 M Ω , were embedded into the endocardial surface.

Experiments were started after 2 h of perfusion with 36.5°C Tyrode's solution. ERP, resting membrane potential (RMP), action potential amplitude (APA), and APD were measured at 20%, 50%, and 90% repolarization (APD20 and APD50 and APD90) recorded before and after the sample was stretched to 110% and 120% of the original

length for 30 min. After the sample had been returned to the original length for 30 min, the above-mentioned ERP and action potential (AP) were recorded again. One cell was recorded at each LAA.

The ERP was measured with 15 basic (S1) stimuli followed by a premature (S2) stimulus at an S1-S2 interval, which was decreased by 1–10 ms decrements from the basic cycle length (BCL). ERP was defined as the longest S1-S2 interval failing to produce a new propagated action potential. ERP was determined twice at each BCL, and the mean of these ERP values was used for data analysis.

Pharmacological Agents. Every potassium channel blocker was administered after a sample was stretched to 120% of the original length. After 30 min, ERP, RMP, APA, APD20, APD50, and APD90 were recorded. Then, the blockers were washed using Tyrode's solution for 30 min, and the ERP and AP were recorded again. Potassium channel blockers that we used included 4-AP (3 mmol/L, Tocris), dofetilide (1 μ mol/L, Tocris), BaCl₂ (10 μ mol/L, Sigma), 293-B (10 μ mol/L, Sigma), DPO-1 (300 nmol/L, Sigma), and glibenclamide (10 μ mol/L, Sigma). The concentration used was 50% of the inhibitory concentration (IC₅₀). To examine the IC₅₀ (dose versus ERP response) in LAA, the tissue was pre-stretched for 30 min, and various doses of each potassium channel blocker were discretely administered on each piece of stretched tissue preparation. The dose-response curves were acquired via logistic equation (data not shown).

Statistical Analysis. Data were expressed as mean $\pm$ standard error of the mean (SEM). Statistical analysis of data was performed by applying one-way analysis of variance (ANOVA) followed by Student-Newman-Keuls post-hoc test. A P -value of less than 0.05 was considered statistically significant.

Results

Effects of Stretch on ERP of Atrial Cardiomyocytes in Guinea Pigs. The ERP of the original length cardiomyocytes in LAA was 132.6 ± 1.8 ms and became 129.7 ± 1.6 ms after LAA was stretched to 110% and 118.9 ± 1.6 ms after LAA was stretched to 120% of the original length for 30 min ($P < 0.05$). APD20, APD50, and APD90 were consistent with the ERP diversification (Table 1). ERP

Table 2. Effect of 4-AP on Stretch-Induced Electrophysiological Changes of Atrial Cardiomyocytes ($n = 6$)

Variables	RMP (mV)	APA (mV)	APD20 (ms)	APD50 (ms)	APD90 (ms)	ERP (ms)
Original	-70.4 ± 1.4	95.0 ± 2.1	40.0 ± 2.2	73.3 ± 2.6	124.4 ± 2.2	128.1 ± 2.4
Stretch (120%)	-69.4 ± 1.6	93.9 ± 1.4	28.8 ± 2.3	57.9 ± 2.7	114.3 ± 2.2	115.9 ± 2.6
Stretch + 4-AP	-68.7 ± 1.2	93.1 ± 1.1	35.8 ± 2.2^a	66.7 ± 2.5^a	122.3 ± 2.4^a	126.5 ± 2.5^a
Wash out	-69.8 ± 1.3	94.3 ± 1.5	26.1 ± 2.2^b	56.2 ± 2.4^b	112.3 ± 2.7^b	113.3 ± 2.6^b

^a $P < 0.01$ vs. Stretch (120%)

^b $P < 0.01$ vs. Stretch + 4-AP.

and repolarization of atrial cardiomyocytes were accelerated in a length-dependent manner. Stretch had no obvious effects on RMP and APA. When the samples were released to the original length, ERP and repolarization were returned to the baseline.

Effects of 4-AP on ERP of Stretched Atrial Cardiomyocytes in Guinea Pigs. The transient outward potassium ion channel (I_{to}) blocker 4-AP lengthened ERP from 115.9 ± 2.6 ms to 126.5 ± 2.5 ms ($P < 0.01$) when LAA was stretched to 120% of the original length. APD20, APD50, and APD90 were also prolonged ($P < 0.01$) when I_{to} was blocked, but RMP and APA were not affected. The above changes of refractoriness and repolarization were reversible after 4-AP was washed away with Tyrode's solution for 30 min ($P < 0.01$) (Table 2, Fig. 1A).

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Effects of Dofetilide on ERP of Stretched Atrial Cardiomyocytes in Guinea Pigs. Dofetilide, a rapid delayed rectifying potassium ion channel (I_{Kr}) blocker, lengthened ERP from 113.0 ± 1.8 ms to 125.7 ± 1.9 ms ($P < 0.01$) when LAA was stretched to 120% of the original length. APD90, APD50, and APD20 were consistent with the ERP diversification ($P < 0.01$) when I_{Kr} was blocked, but RMP and APA remained unaffected ($P > 0.05$). The above changes of refractoriness and repolarization, except those observed for APD20, could be nullified after the blocker was washed away with Tyrode's solution for 30 min ($P < 0.01$) (Table 3, Fig. 1B).

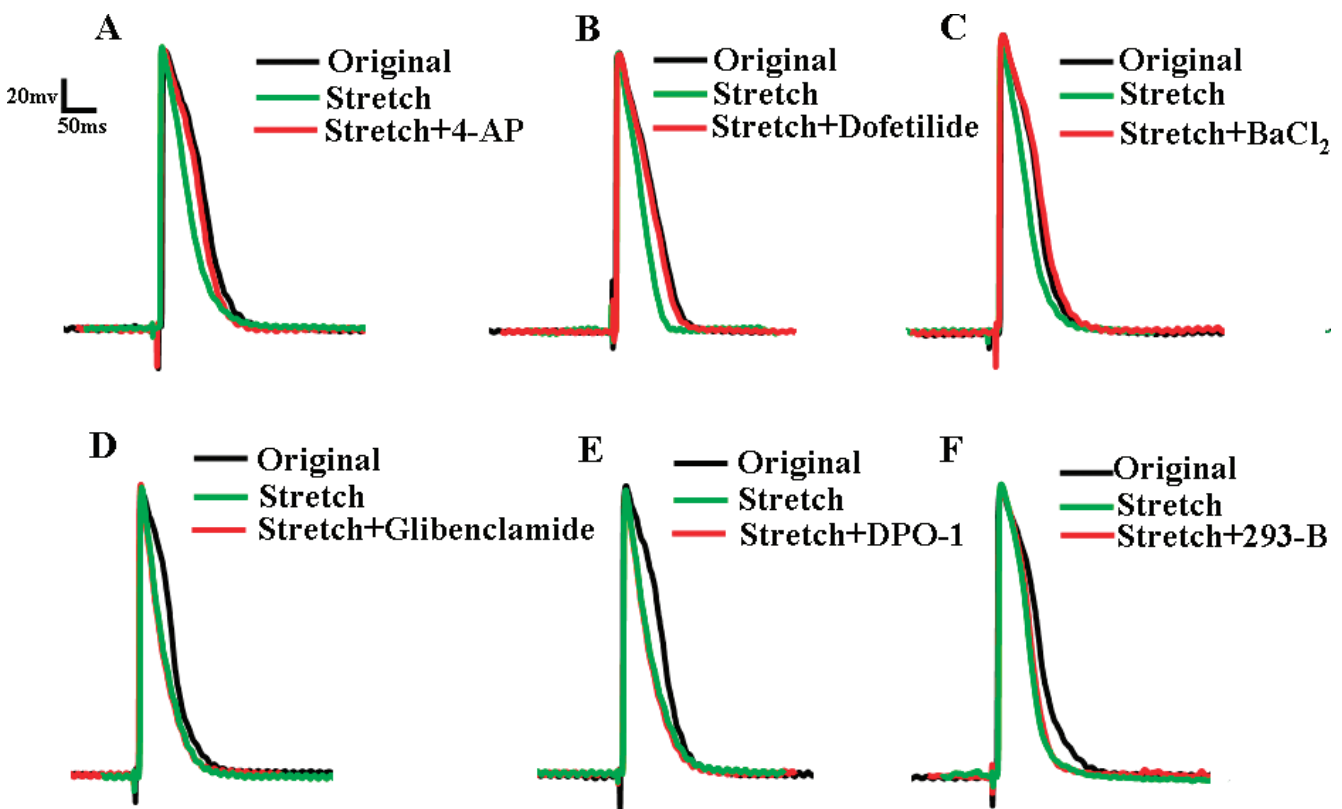


Figure 1. Effects of potassium channel blockers on the action potential (AP) configuration of atrial cardiomyocytes induced by stretch. (A) The effect of 4-AP on the AP configuration of atrial cardiomyocytes induced by stretch. (B) The effect of dofetilide on the AP configuration of atrial cardiomyocytes induced by stretch. (C) The effect of $BaCl_2$ on the AP configuration of atrial cardiomyocytes induced by stretch. (D) The effect of glibenclamide on the AP configuration of atrial cardiomyocytes induced by stretch. (E) The effect of 293-B on the AP configuration of atrial cardiomyocytes induced by stretch. (F) The effect of DPO-1 on the AP configuration of atrial cardiomyocytes induced by stretch.

Table 3. Effect of Dofetilide on Stretch-Induced Electrophysiological Changes of Atrial Cardiomyocytes ($n = 6$)

Variables	RMP (mV)	APA (mV)	APD20 (ms)	APD50 (ms)	APD90 (ms)	ERP (ms)
Original	-70.9 ± 0.8	96.9 ± 1.7	37.5 ± 1.1	69.7 ± 2.3	123.6 ± 2.0	125.7 ± 1.7
Stretch (120%)	-70.1 ± 1.3	96.5 ± 1.1	26.8 ± 1.5	55.1 ± 2.7	112.5 ± 2.8	113.0 ± 1.8
Stretch+Dofetilide	-69.2 ± 0.9	95.6 ± 1.1	31.4 ± 1.6	68.4 ± 2.1^a	123.8 ± 2.7^a	125.7 ± 1.9^a
Wash out	-69.1 ± 0.9	95.9 ± 1.8	29.4 ± 1.5	54.0 ± 2.2^b	111.2 ± 2.6^b	114.2 ± 2.2^b

^a $P < 0.01$ vs. Stretch (120%).^b $P < 0.01$ vs. Stretch + Dofetilide.**Table 4.** Effect of BaCl₂ on Stretch-Induced Electrophysiological Changes of Atrial Cardiomyocytes ($n = 6$)

Variables	RMP (mV)	APA (mV)	APD20 (ms)	APD50 (ms)	APD90 (ms)	ERP (ms)
Original	-70.4 ± 0.8	96.0 ± 1.6	36.5 ± 1.2	69.9 ± 1.4	121.7 ± 1.7	122.3 ± 1.1
Stretch (120%)	-69.8 ± 0.7	95.2 ± 1.6	25.4 ± 1.0	54.9 ± 1.3	111.2 ± 1.6	109.7 ± 1.3
Stretch + BaCl ₂	-69.7 ± 0.9	95.4 ± 2.0	27.0 ± 1.3	62.7 ± 1.7^a	134.9 ± 2.2^a	136.5 ± 1.8^a
Wash out	-70.0 ± 0.8	95.6 ± 1.8	25.3 ± 1.0	53.8 ± 1.6^b	113.6 ± 1.8^b	111.8 ± 1.5^b

^a $P < 0.01$ vs. Stretch (120%).^b $P < 0.01$ vs. Stretch + BaCl₂.

Effects of BaCl₂ on ERP of Stretched Atrial Cardiomyocytes in Guinea Pigs. BaCl₂, an inward rectifying potassium ion channel (I_{K1}) blocker, lengthened ERP from 109.7 ± 1.3 ms to 136.5 ± 1.8 ms ($P < 0.01$) when LAA was stretched to 120% of the original length. APD90 and APD50 were consistent with the ERP diversification ($P < 0.01$) when I_{K1} was blocked, but APD20, RMP, and APA remained unaffected ($P > 0.05$). The above changes of refractoriness and repolarization disappeared after the blocker was washed away with Tyrode's solution for 30 min ($P < 0.01$) (Table 4, Fig. 1C).

Effects of Glibenclamide, 293-B and DPO-1 on ERP of Stretched Atrial Cardiomyocytes in Guinea Pigs. Glibenclamide, an ATP-sensitive potassium ion channel (I_{KATP}) blocker, 293-B, a slow-delayed rectifying potassium channel (I_{Ks}) blocker, and DPO-1, an ultra-rapid delayed rectifying potassium ion channel (I_{Kur}) blocker, all had no effects on the alteration of refractoriness and repolarization of atrial cardiomyocytes induced by the mechanical stretching (Fig. 1D–F, Figs. 2–4).

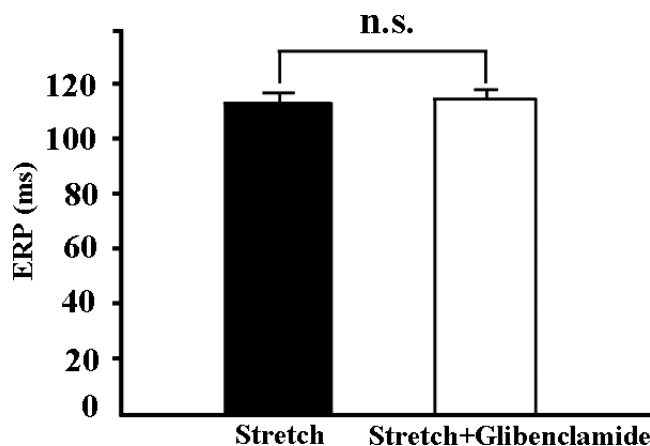
Discussion

The major findings of the present study are as follows: (1) stretch accelerated repolarization of atrial cardiomyocytes and also shortened their ERP; (2) I_{to}, I_{Kr}, and I_{K1} blockers could effectively counteract shortening of APD and ERP induced by stretch; (3) I_{Ks}, I_{Kur}, and I_{KATP} blockers had no effects on APD and ERP changes induced by stretch.

The shorter the ERP, the higher the probability that multiple reentrant circuits exist simultaneously in atrial myocardium. The presence of these multiple reentrant circuits may increase the stability of AF (16, 17). In accordance with other studies, the results of the present study indicated that atrial ERP was also significantly

shortened by stretch (3, 7, 14). Cardiac repolarization and refractoriness is partly determined by potassium channels (11–13). The shortening of APD and ERP can be explained by increased K⁺ currents, indicating that the blockage of certain potassium channels can counteract the effects (2).

As for stretch-induced I_{K1} current alteration, in one of our previous related studies, we found that I_{K1} currents were significantly larger under stretch in the hypotonic solution than under nonstretch in the iso-osmotic solution (17). In the present study, I_{K1} blockers were found to effectively counteract the shortening of APD and ERP induced by stretch. Increased I_{K1} density has been found to contribute to the occurrence of AF (15, 16). It has also been reported that the stretch-induced increase of I_{K1} current corresponds to the observations in chronic AF in humans (15, 16). Our results, taken together with these findings, indicate that I_{K1} blockers might be effective in the treatment of stretch-

**Figure 2.** The effect of glibenclamide on the ERP of atrial cardiomyocytes induced by stretch. The bars represent the mean $\pm$ SD ($n = 6$). n.s., not significant.

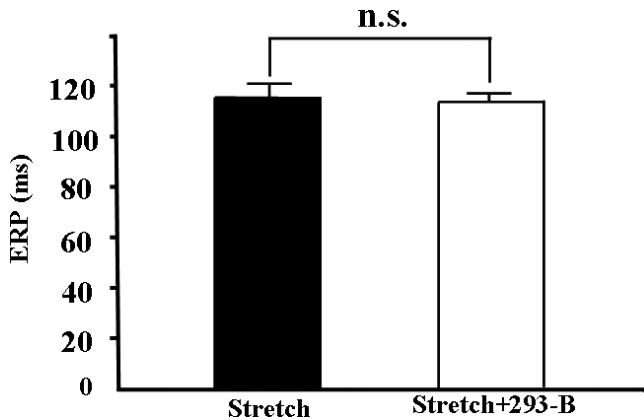


Figure 3. The effect of 293-B on the effective refractory period (ERP) of atrial cardiomyocytes induced by stretch. The bars represent the mean $\pm$ SD ($n = 6$). n.s., not significant.

induced AF. However, Van Wagoner et al. (18) have found that the resting potential and I_{K1} density were not altered in dilated cells compared with nondilated human atria, and this may be caused by the variability of the I_{K1} response in different populations of patients with atrial disease.

I_{to} underlies the 'notch' during the initial phase of repolarization that is often evident in ventricular action potentials (3). It also influences the overall duration of the action potential, albeit indirectly (3). Downregulation of I_{to} has been reported in patients with persistent AF (1–3). Two reasons may explain why the I_{to} blocker could counteract the refractoriness and repolarization alteration caused by stretch in this study. First, reducing I_{to} may result in a decrease in another current that effects repolarization and refractoriness. Second, differences between the results reported here and those of previous studies could be caused by species differences.

Not all blockage of potassium channels could counteract the effects induced by stretch. The I_{Kr} blocker used in the present study was found to counteract the refractoriness and repolarization alteration caused by stretch, whereas the I_{Ks} blocker had no effects. I_{KATP} has been previously demonstrated to be activated by SACs and is involved in the protection from stretch-induced cardiac damage and arrhythmia (2, 19). I_{KATP} amplitude is increased under ischemic conditions in cells from AF patients, indicating that it is an important contributor to ischemia-induced electrophysiological abnormalities (2). The data of this study show that the I_{KATP} blocker had no effects on ERP alteration caused by stretch, indicating that the blockade of I_{KATP} might be unable to prevent stretch-induced AF. I_{Kur} is a strong atrial-selective expressed channel whose blockade is regarded as a potential target for atrial-selective antiarrhythmic drugs (19, 20). However, the I_{Kur} blocker had no effect on ERP, implying that I_{Kur} blockade has no effect on stretch-induced AF. Of course, it may also be caused by the different extent of stretch used and/or species differences.

Of note, the effect of stretch-activated ion channels

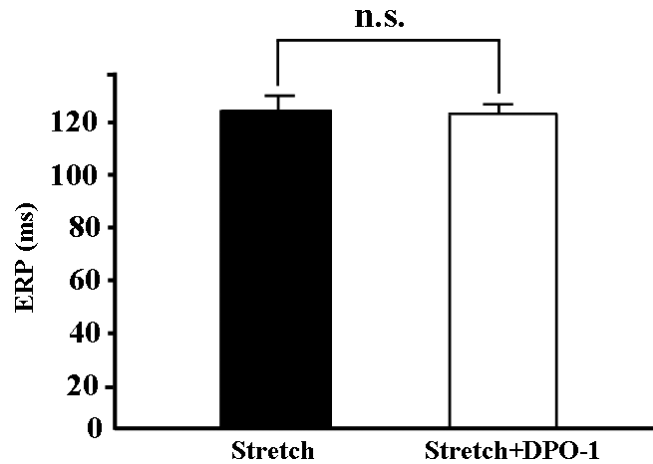


Figure 4. The effect of DPO-1 on the ERP of atrial cardiomyocytes induced by stretch. The bars represent the mean $\pm$ SD ($n = 6$). n.s., not significant.

(SACs), which are thought to play an important role in promoting arrhythmias during stretch (8, 21), was not evaluated in this study for two reasons. First, selective blockers are not known at present (10). For example, gadolinium blocks SACs and also blocks L-type Ca^{2+} channels and delayed rectifier K^{+} channels (8, 10, 21). Therefore, the SAC blockers previously used are fairly unspecific (8, 10). Second, from the physiological point of view, if SACs exist in the cardiac myocytes, their major function would be participation in the normal stretch-dependent changes in the heart muscle (such as Frank-Starling relation), rather than generation of pathological phenomena (10), and this is out of the scope of the present study.

Disappointingly, current therapy of AF is suboptimal (1–3). Drugs to maintain sinus rhythm by altering cardiac electrical properties have incomplete efficacy and may also increase the mortality caused by proarrhythmia, as they are not specific for atrial electrical activity (2–4). For example, dofetilide, the I_{Kr} blocker, has been used to treat various kinds of atrial arrhythmia, but unfortunately, these drugs predictably evoke prolongation of the QT interval, which is sufficient to cause dangerous ventricular arrhythmias in 5–7% of recipients (11). Therefore, finding new therapies for AF is imperative. Based on the results of this present study, it is possible that the prevention of stretch-induced AF may be achieved with better ion channel-targeted drugs, especially for I_{to} , I_{Kr} , and I_{K1} .

In summary, the major finding is that stretch may accelerate repolarization of atrial cardiomyocytes and shorten the ERP, and I_{to} , I_{Kr} , and I_{K1} blockers could effectively counteract the effect caused by stretch.

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