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Streptomycin inhibits electrophysiological changes induced by stretching of chronically infarcted rat hearts*

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Abstract: Objective: To investigate stretch-induced electrophysiological changes in chronically infarcted hearts and the effect of streptomycin (SM) on these changes *in vivo*. Methods: Sixty Wistar rats were divided randomly into four groups: a control group (*n*=15), an SM group (*n*=15), a myocardial infarction (MI) group (*n*=15), and an MI+SM group (*n*=15). Chronic MI was obtained by ligating the left anterior descending branch (LAD) of rat hearts for eight weeks. The *in vivo* blockade of stretch-activated ion channels (SACs) was achieved by intramuscular injection of SM (180 mg/(kg·d)) for seven days after operation. The hearts were stretched for 5 s by occlusion of the aortic arch. Suction electrodes were placed on the anterior wall of left ventricle to record the monophasic action potential (MAP). The effect of stretching was examined by assessing the 90% monophasic action potential duration ($MAPD_{90}$), premature ventricular beats (PVBs), and ventricular tachycardia (VT). Results: The $MAPD_{90}$ decreased during stretching in both the control (from (50.27±5.61) ms to (46.27±4.51) ms, P<0.05) and MI groups (from (65.47±6.38) ms to (57.47±5.76 ms), P<0.01). SM inhibited the decrease in $MAPD_{90}$ during inflation ((46.27±4.51) ms vs. (49.53±3.52) ms, P<0.05 in normal hearts; (57.47±5.76) ms vs. (61.87±5.33) ms, P<0.05 in MI hearts). The occurrence of PVBs and VT in the MI group increased compared with that in the control group (PVB: 7.93±1.66 vs. 1.80±0.86, P<0.01; VT: 7 vs. 1, P<0.05). SM decreased the occurrence of PVBs in both normal and MI hearts (0.93±0.59 vs. 1.80±0.86 in normal hearts, P<0.05; 5.40±1.18 vs. 7.93±1.66 in MI hearts, P<0.01). Conclusions: Stretch-induced $MAPD_{90}$ changes and arrhythmias were observed in chronically infarcted myocardium. The use of SM *in vivo* decreased the incidence of PVBs but not of VT. This suggests that SACs may be involved in mechanoelectric feedback (MEF), but that there might be other mechanisms involved in causing VT in chronic MI.

Key words: Arrhythmia, Mechanoelectric feedback, Monophasic action potential, Myocardial infarction, Streptomycin
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1 Introduction

There is a close relationship between malignant ventricular arrhythmias and myocardial infarction (MI) (Haugaa *et al.*, 2010), which leads to high cardiovascular mortality (Wang, 2012). It is well recognized that mechanical restitution and regional inhomogeneity in contractility act as foci for arrhythmias (Thygesen and Uretsky, 2004; Ashikaga *et al.*, 2005) through a process known as mechanoelectric feedback (MEF). In chronic MI, scar tissue is surrounded by normal or ischemic myocardium, and greater stretch occurs than in normal myocardium (Bertini *et al.*, 2010). Previous studies also verified that MEF can be increased by chronic MI (Kiseleva *et al.*, 2000), contributing to the appearance of arrhythmias. We inferred that electrophysiological changes induced by stretch in normal hearts, shortened action potential duration (APD), the occurrence of after-depolarization, and premature beats (Kiseleva *et al.*, 2000; Ravens, 2003; Taggart and Lab, 2008) might be observed in chronically

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infarcted myocardium. Many studies have demonstrated that stretch-activated ion channels (SACs) have a crucial role to perform in MEF, though details of the mechanism are unclear (Garan *et al.*, 2005; Lab, 2006).

Streptomycin (SM), a blocker of SACs, has been known to inhibit the activities of SACs in single cell, tissue, and intact preparations in various species (Lab, 2006). It can decrease the occurrence of arrhythmias induced by changes in ventricular wall-stress in isolated rat hearts (Salmon *et al.*, 1997). Eckardt *et al*. (2001) studied Langendorff-perfused rabbit hearts and found that SM (200 μmol/L) could inhibit the shortened repolarization induced by stretching. The dominant frequency of ventricular fibrillation (VF) induced by stretching decreases following SM treatment in rabbit hearts (Trapero *et al.*, 2008). SM also prevents stretch-related vulnerability to atrial fibrillation (Ninio and Saint, 2008). In hearts from hypertensive rats, Kim *et al*. (2012) recently found that 100 μmol/L SM could reduce stretch-induced ectopic heartbeats by increasing the threshold for stretch-induced arrhythmias.

However, the effect of blocking of SACs with SM has seldom been observed *in vivo*, and results are often contradictory. Cooper and Kohl (2005) reported that SM could not block chronotropy in the spontaneous pacemaking rate induced by stretching, and further questioned the *in situ* utility of SM for acute blocking of mechanosensitive mechanisms. Garan *et al*. (2005) found that SM reduced ST segment elevation following impact in swine but did not reduce the frequency of VF. Using skeletal muscle, Yeung *et al*. (2005) and Spangenburg and McBride (2006) found that oral SM *in vivo* could block the activities of SACs in the rat and mouse, respectively. However, there has been no analogous study on myocardium.

The aim of this study was to observe the effect of stretching on the monophasic action potential (MAP) and the effect of the application of SM *in vivo* on electrophysiological changes in chronically infarcted rat hearts.

2 Materials and methods

2.1 Preparation of MI model

The study was performed in accordance with the rules of *The Care and Use of Laboratory Animals* issued by the US National Institute of Health (NIH Publication No. 85-23, revised in 1985).

Sixty Wistar rats (regardless of their genders, 180–224 g) were chosen for the experiment. Each rat, anaesthetized by intraperitoneal injection using sodium pentobarbital (40–50 mg/kg) and heparin (1000 U/kg), was intubated and then connected to a respirator. Artificial respiration was provided during the whole surgical process (breathing rate 60 min^{-1}, tidal volume 30 ml/100 mg). Electrocardiograms (ECG; limb leads including I, II, III, aVR, aVL, aVF) were recorded from electrodes attached to the limbs of each rat. Briefly, MI was obtained by ligating the left anterior descending branch (LAD) of the coronary artery. First, the heart was exteriorized between the 3rd and 4th costal bones of the left sternal border. Second, the LAD was ligated between the pulmonary conus and the left auricle. Successful ligature of the LAD was verified by regional myocardial cyanosis and ST elevation in the ECG. Third, the heart was replaced and the cut was stitched. Sham-operated animals were operated following the procedure mentioned above, but without ligation of the LAD. The surviving rats were kept in a cage and fed with a full diet and water.

Sham-operated animals were divided at random into two groups: a control group (n=15) in which experiments were carried out after 8 weeks and an SM group (n=15) in which after 7 weeks, the rats were injected intramuscularly with SM (Merro Pharmaceuticals Companies; 180 mg/(kg·d)) for 7 d. Experiments were then conducted. MI animals were also divided into two groups: an MI group (n=15) in which experiments were carried out 8 weeks after ligature of the LAD and an MI+SM group (n=15) in which, after ligation of the LAD for 7 weeks, the rats were injected intramuscularly with SM (180 mg/(kg·d)) for 7 d. Experiments were then conducted.

2.2 Recording

Each animal was anaesthetized and ventilated as mentioned above. ECG was recorded during the whole experiment. The right common carotid artery was dissociated. A catheter was connected to a pressure transducer (YP500, Gaobeidian, China), which was inserted into the left ventricle (LV) via the right common carotid artery and aorta by catheterization to measure the pressure of the ventricle. The distance between the end of the catheter and the transducer was minimized to decrease system dampening. Thoracotomy was performed. The heart and aortic arch were revealed. A suction electrode, placed on the

anterior wall of the LV, was used to detect LV MAP (Fu *et al.*, 2007).

2.3 Protocols

After stabilization for 15 min, the heart was stretched by an occlusion of the aortic arch for 5 s, followed by unclamping of the aortic arch. The 90% monophasic action potential duration ($MAPD_{90}$), LV pressure, premature ventricular beats (PVBs), and ventricular tachycardia (VT) were monitored during 5 s of stretching.

2.4 Data analysis

The measurement and analysis of $MAPD_{90}$ (in ms) were conducted according to the criteria of Fu *et al.* (2007). Every five beats, one MAP was analyzed and then averages were calculated. Stretch-induced arrhythmias (SIAs) were defined according to the guidelines of the Lambeth Convention (Curtis *et al.*, 2013). Data were analyzed using SPSS 13.0 (Statistical Package for the Social Sciences 13.0, SPSS Company, USA) by an independent University-based statistician. Quantitative data, expressed as mean± standard deviation (SD), were compared with analysis of variance (ANOVA). A χ^2 test was used for qualitative data. $P<0.05$ was considered statistically significant.

3 Results

3.1 Effect of stretching on $MAPD_{90}$

During the occlusion of the aortic arch, the $MAPD_{90}$ decreased, compared with the basal condition in the control group ((50.27±5.61) ms vs. (46.27±4.51) ms, $P<0.05$) and in the MI group ((65.47±6.38) ms vs. (57.47±5.76) ms, $P<0.01$) (Fig. 1). The $MAPD_{90}$ increased significantly compared with the control groups after ligation of the LAD ((65.47±6.38) ms vs. (50.27±5.61) ms, $P<0.01$) and during stretching ((57.47±5.76) ms vs. (46.27±4.51) ms, $P<0.01$) (Fig. 1).

3.2 Effect of SM on $MAPD_{90}$ changes during stretching

After the treatment with SM, the $MAPD_{90}$ showed no significant changes from basal conditions either in normal ((50.27±5.61) ms vs. (50.33±3.62) ms, $P>0.05$) or infarcted rat hearts ((65.47±6.38) ms vs. (63.20±6.32) ms, $P>0.05$) (Fig. 1). However, SM inhibited the stretch-induced decrease in $MAPD_{90}$ during the occlusion of the aortic arch, both in the normal (compared with the basal conditions, (49.53±3.52) ms vs. (50.33±3.62) ms, $P>0.05$) and MI hearts (compared with the basal conditions, (61.87±5.33) ms vs. (63.20±6.32) ms, $P>0.05$). SM partly reversed the decrease in $MAPD_{90}$ induced by stretching in the normal hearts ((49.53±3.52) ms vs. (46.27±4.51) ms, $P<0.05$) and in the infarcted rat hearts ((61.87±5.33) ms vs. (57.47±5.76) ms, $P<0.05$) (Fig. 1).

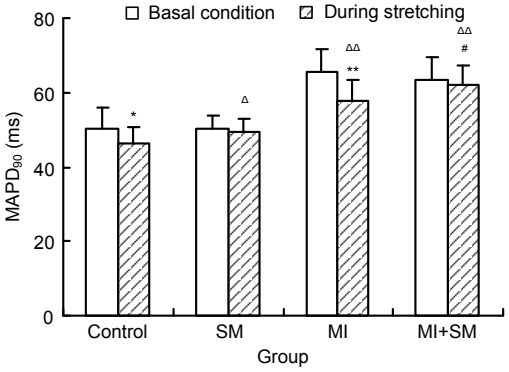

Fig. 1 Influence of streptomycin (SM) on 90% monophasic action potential duration ($MAPD_{90}$) in control and myocardial infarction (MI) groups during stretching (the occlusion of the aortic arch for 5 s)

$MAPD_{90}$ decreased in the control group during stretching ($^{*}P<0.05$) and in the MI group ($^{**}P<0.01$), compared with that under basic conditions. SM had no influence on $MAPD_{90}$ in either normal or infarcted rat hearts under basic conditions, but SM did inhibit the decrease in $MAPD_{90}$ induced by stretching ($^{\Delta}P<0.05$, $^{\Delta\Delta}P<0.01$, compared with the control group; $^{\#}P<0.05$, compared with the MI group). Data are expressed as mean±SD (n=15)

3.3 Effect of SM on SIAs

The PVBs appeared during the occlusion of the aorta. The number of PVBs was counted during the 5 s of occlusion of the aorta. The incidence of PVBs in the control group was observed during stretching (1.80±0.86). After ligation of the LAD for eight weeks, the incidence showed a marked and significant increase (7.93±1.66 in the MI group vs. 1.80±0.86 in the control group, $P<0.01$). SM obviously reduced the number of PVBs caused by the occlusion of the aorta (1.80±0.86 vs. 0.93±0.59 in normal hearts, $P<0.05$; 7.93±1.66 vs. 5.40±1.18 in infarcted hearts, $P<0.01$) (Table 1). Signal collecting systems recorded the MAP figures (Fig. 2).

Table 1 Effect of streptomycin (SM) on premature ventricular beats (PVBs) induced by stretching for 5 s

Group	Number of PVBs
Control	1.80±0.86
SM	0.93±0.59*
MI	7.93±1.66**
MI+SM	5.40±1.18Δ

After ligation of the left anterior descending artery for eight weeks, the number of PVBs obviously increased during the occlusion of the aortic arch for 5 s (** P<0.01). The occurrence of PVBs significantly decreased with the use of SM, both in normal (* P<0.05) and infarcted hearts (Δ P<0.01). Data are expressed as mean±SD (n=15)

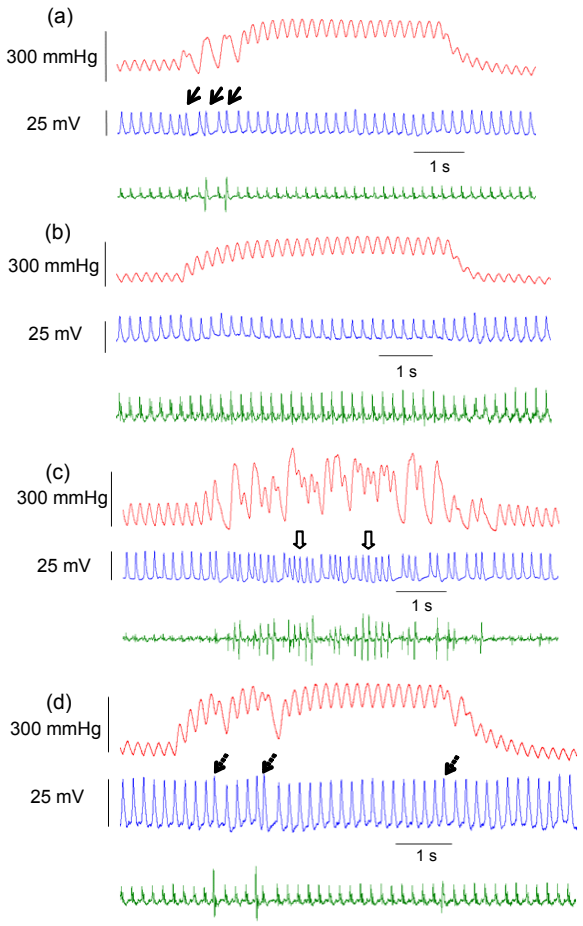

Fig. 2 Monophasic action potentials (MAPs) and stretch-induced arrhythmias in chronically infarcted rat hearts

Upper figure: left ventricular pressure (LVP); Middle figure: MAP; Lower figure: ECG. (a) The occurrence of premature ventricular beats (PVBs) (thick arrows) during stretching in normal hearts; (b) Streptomycin (SM) inhibited the appearance of PVBs induced by stretching; (c) The number of PVBs increased significantly after ligation of the left anterior descending artery for eight weeks, and ventricular tachycardia (arrows with open hole) also occurred; (d) The occurrence of arrhythmias (arrows with dotted line) was reduced by pretreatment with SM

During the occlusion of the aortic arch for 5 s, the number of VT in the control group was 1, whereas it increased to 7 in the MI group. After treatment with SM, the number of VT decreased to 0 in the SM group and to 3 in the MI+SM group. The incidence of VT was higher than that in the control group (P<0.05). SM decreased the occurrence of VT, but there was no significant difference between incidence in the MI+SM group and the MI group (P>0.05) (Table 2).

Table 2 Effect of streptomycin (SM) on the occurrence of ventricular tachycardia (VT) during stretching for 5 s

Group	Number of hearts with VT	Number of hearts without VT
Control	1	14
SM	0	15
MI	7*	8
MI+SM	3	12

The number of hearts with VT increased with stretching after ligation of the left anterior descending artery for eight weeks (* P<0.05). SM decreased the occurrence of VT, but the difference was not significant (P>0.05)

4 Discussion

The present study found that the application of SM *in vivo* could inhibit changes in $MAPD_{90}$ and decrease the incidence of PVBs induced by stretching of chronically infarcted rat hearts. However, SM did not reduce the occurrence of VT, indicating the involvement of SACs in the genesis of stretch-induced PVBs in chronic MI, but suggesting a more complicated situation for stretch-induced VT.

4.1 Changes in $MAPD_{90}$ and arrhythmias induced by stretching

Changes in MAPD caused by transiently increasing LV pressure have been reported in the normal myocardium of many species (Reiter *et al.*, 1997; Takagi *et al.*, 1999; Lerman *et al.*, 2001). Consistent with the results of earlier studies, the $MAPD_{90}$ of the LV was shortened during transient aortic occlusion in this study. Furthermore, we found that the stretch-induced decrease in $MAPD_{90}$ *in vivo* also had happened in the chronic MI rat hearts. By using a slice from the LV after MI treatment for five weeks, Kiseleva *et al*. (2000) found that the sensitivity of the

membrane potential and depolarization to stretch increased. Fu *et al.* (2007) verified that the phenomenon of MEF increased in acute myocardium infarction (AMI) as well. The contraction force of ischaemic and infarcted myocardium was lower than that of surrounding normal myocardium after MI. So, stretch exists between the normal and ischemic myocardia. Likewise, stretch also exists between the infarcted and ischemic myocardia in chronic MI. In the present study, more PVBs and VT occurred in infarcted myocardium with occlusion of the aorta, which is consistent with previous results (Horner *et al.*, 1996).

4.2 Effects of the application of SM *in vivo* on $MAPD_{90}$

In single cardiomyocytes (Belus and White, 2003) and multicellular preparations (Eckardt *et al.*, 2000; Spangenburg and McBride, 2006), SM has been verified to be an effective blocker of SACs. This study confirmed that the stretch-induced decrease in $MAPD_{90}$ in chronic MI could be pharmacologically inhibited by an SAC blocker. SM had no effect on the $MAPD_{90}$ under basic conditions, but effectively inhibited the shortening of the $MAPD_{90}$ induced by transient aortic occlusion in both normal and chronically infarcted hearts. Based on these results and the characteristics of MEF, we inferred that: (1) in chronic MI, the activities of SACs were involved in the stretch-induced changes in the $MAPD_{90}$; (2) treatment with SM *in vivo* can inhibit the activities of SACs.

4.3 Effects of the application of SM *in vivo* on SIAs

SM showed different effects on PVBs and VT. SM decreased the occurrence of PVBs caused by stretching. The Ca^{2+} cycle and the activities of SACs are the main mechanisms of SIAs (Lab, 1996). In short, the activities of SACs during stretching caused an increase in intracellular Ca^{2+} ($[Ca^{2+}]_i$), which leads to after-depolarization and subsequent triggered activity (Fu *et al.*, 2007). The mechanism of the anti-arrhythmia effect of SM might be that by blocking SACs, it inhibits the increase in $[Ca^{2+}]_i$.

On the other hand, SM did not alter the occurrence of VT induced by aortic occlusion. There may have been several possible reasons for this: (1) the lack of a significant difference in this study may have been because of the small sample size; (2) absorption efficiency may have varied among different tissues following the application of SM *in vivo*, causing our results to differ from those of previous studies (Yeung *et al.*, 2005; Spangenburg and McBride, 2006); (3) besides SACs, a more complicated mechanism may be involved in stretch-induced VT.

5 Conclusions

Stretch-induced $MAPD_{90}$ changes and arrhythmias via MEF were observed in chronically infarcted myocardium. The use of SM *in vivo* decreased the incidence rate of PVBs but not VT, suggesting the involvement of SACs in MEF but that there might be other mechanisms involved in the formation of VT in chronically infarcted myocardium.

The results of our study revealed increased MEF in chronic MI and the effectiveness of SM *in vivo* in minimizing certain electrophysiological changes during stretching. However, because of the risk of hearing and kidney damage caused by SM, further pharmacological studies are needed to find SM analogues which are safe for clinical application. Moreover, other studies will be necessary to explore further the mechanism of action of SIAs because other mechanosensitive ion channels in myocardium (Healy and McCulloch, 2005) may also be involved in stretch-induced electrical activity abnormalities, especially VT.

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Compliance with ethics guidelines

Jun-xian CAO, Lu FU, Qian-ping GAO, Rong-sheng XIE, and Fan QU declare that they have no conflict of interest.

All institutional and national guidelines for the care and use of laboratory animals were followed.

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中文概要：

本文题目：链霉素抑制慢性心肌梗死大鼠心脏牵张时的电生理改变

Streptomycin inhibits electrophysiological changes induced by stretching of chronically infarcted rat hearts

研究目的：以往研究发现链霉素作为牵张激活离子通道阻断剂，可抑制机械电反馈时心脏的电生理效应，但多为离体研究。由于慢性心肌梗死时心肌细胞间存在较为明确的牵拉，故本研究探讨了在大鼠体内应用链霉素是否可以抑制慢性心肌梗死大鼠心脏牵张诱导的电生理改变。

创新要点：首次探讨了在大鼠体内应用链霉素对慢性心梗时心脏机械电反馈现象的影响。

研究方法：60 只 Wistar 大鼠随机分为 4 组：对照组（*n*=15）、链霉素组（*n*=15）、心梗组（*n*=15）和心梗＋链霉素组（*n*=15）。结扎左前降支（LAD）8 周制备慢性心梗模型，术后肌注链霉素（180 mg/(kg·d)）7 天后，钳夹主动脉 5 秒牵张心脏，观察牵张效应包括 90%单相动作电位时程（$MAPD_{90}$）、室性期前收缩（PVB）、室性心动过速（VT）等。

重要结论：研究结果发现牵张使得对照组（(50.27±5.61) ms vs. (46.27±4.51) ms, $P<0.05$）和心梗组（(65.47±6.38) ms vs. (57.47±5.76) ms, $P<0.01$）大鼠心脏 $MAPD_{90}$ 缩短。链霉素可抑制牵张引起的正常（(46.27±4.51) ms vs. (49.53±3.52) ms, $P<0.05$）和梗死心肌（(57.47±5.76) ms vs. (61.87±5.33) ms, $P<0.05$）$MAPD_{90}$ 的缩短（见图 1）。牵张后心梗组大鼠心肌 PVB（7.93±1.66 vs. 1.80±0.86, $P<0.01$）和 VT（7 vs. 1, $P<0.05$）的发生较对照组增多。链霉素可抑制正常（0.93±0.59 vs. 1.80±0.86, $P<0.05$）和梗死心肌（5.40±1.18 vs. 7.93±1.66, $P<0.01$）PVB 的发生。以上结果表明，牵张诱导慢性梗死心肌出现 $MAPD_{90}$ 的改变并产生心律失常。在大鼠体内应用链霉素可降低 PVB 的发生但对 VT 无影响。因此，牵张激活离子通道可能参与到慢性心梗的机械电反馈中，同时可能有其他机制参与到牵张诱导的 VT 中。

关键词组：心律失常；机械电反馈；单相动作电位；心肌梗死；链霉素