Ventricular tachyarrhythmias in rats with acute myocardial infarction involves activation of small-conductance Ca$^{2+}$-activated K$^+$ channels

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1Department of Cardiology, Affiliated Hospital of Nantong University, Nantong, Jiangsu, People’s Republic of China; 2Biomolecular Science Center, Burnett School of Biomedical Sciences College of Medicine, University of Central Florida, Orlando, Florida; and 3Department of Kinesiology and Integrative Physiology, Michigan Technological University, Houghton, Michigan

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Ventricular tachyarrhythmias in rats with acute myocardial infarction involves activation of small-conductance Ca$^{2+}$-activated K$^+$ channels. Am J Physiol Heart Circ Physiol 304: H118–H130, 2013. First published October 19, 2012; doi:10.1152/ajpheart.00820.2011.—In vitro experiments have shown that the upregulation of small-conductance Ca$^{2+}$-activated K$^+$ (SK) channels in ventricular epicardial myocytes is responsible for spontaneous ventricular fibrillation (VF) in failing ventricles. However, the role of SK channels in regulating VF has not yet been described in vivo acute myocardial infarction (AMI) animals. The present study determined the role of SK channels in regulating spontaneous sustained ventricular tachycardia (SVT) and VF, the inducibility of ventricular tachyarrhythmias, and the effect of inhibition of SK channels on spontaneous SVT/VF and electrical ventricular instability in AMI rats. AMI was induced by ligation of the left anterior descending coronary artery in anesthetized rats. Spontaneous SVT/VF was analyzed, and programmed electrical stimulation was performed to evaluate the inducibility of ventricular tachyarrhythmias, ventricular effective refractory period (VERP), and VF threshold (VFT). In AMI, the duration and episodes of spontaneous SVT/VF were increased, and the inducibility of ventricular tachyarrhythmias was elevated. Pretreatment in the AMI group with the SK channel blocker apamin or UCL-1684 significantly reduced SVT/VF and inducibility of ventricular tachyarrhythmias ($P < 0.05$). Various doses of apamin (7.5, 22.5, 37.5, and 75.0 μg/kg iv) inhibited SVT/VF and the inducibility of ventricular tachyarrhythmias in a dose-dependent manner. Notably, no effects were observed in sham-operated controls. Additionally, VERP was shortened in AMI animals. Pretreatment in AMI animals with the SK channel blocker significantly prolonged VERP ($P < 0.05$). No effects were observed in sham-operated controls. Furthermore, VFT was reduced in AMI animals, and block of SK channels increased VFT in AMI animals, but, again, this was without effect in sham-operated controls. Finally, the monophasic inhibition of SK channels increased VFT in AMI animals, but, again, this was not observed in sham-operated controls. Furthermore, VFT was reduced in AMI animals, and block of SK channels increased VFT in AMI animals, but, again, this was without effect in sham-operated controls. We conclude that the activation of SK channels may underlie the mechanisms of spontaneous SVT/VF and susceptibility to ventricular tachyarrhythmias in AMI. Inhibition of SK channels normalized the shortening of MABP in the MI area, which may contribute to the inhibitory effect on spontaneous SVT/VF and inducibility of ventricular tachyarrhythmias in AMI.

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ISCHEMIC HEART DISEASE is the leading cause of death in the industrialized world (19). It has been well documented that sudden cardiac death is the first clinical manifestation among 25% of patients with myocardial ischemia or myocardial infarction (MI) (26), and ventricular fibrillation (VF) is the most common underlying cause (22). Therefore, prevention and therapy of VF are critical for reducing the mortality induced by acute MI (AMI). Factors of arrhythmogenesis associated with AMI have been studied for many years. The occurrence of potentially lethal arrhythmias is the end result of a cascade of pathophysiological abnormalities that result from complex interactions among coronary vascular events (36), myocardial injury (29, 33), and changes in autonomic tone (53) as well as an altered ionic state of the myocardium (15, 46).

Molecular identification and functional studies have reported the existence of small-conductance (SK) Ca$^{2+}$-activated K$^+$ (KCa) channels in cardiac myocytes from the human, mouse (51), guinea pig (14), and rabbit (11). Furthermore, there is growing evidence indicating that alterations of SK channel ionic currents underlie the mechanisms of both atrial fibrillation (14) and VF (11). For example, inhibition of SK channels prolongs the atrial effective refractory period without affecting the QT interval and also prevents and terminates atrial fibrillation ex vivo and in vivo (14). In contrast, another study (28) reported that knockout of SK2 channels prolongs action potential duration (APD) and induces atrial fibrillation (28). Very recently, an in vitro study (11) reported that blockade of SK channels with apamin reduced APD shortening and spontaneous VF induced by postspacing or postshock in a tachycardia-induced heart failure model. Additionally, in the same study (11), the density of SK currents in epicardial cardiac myocytes was increased in failing ventricles. These data indicate that heart failure heterogeneously increases the sensitivity of SK channels to intracellular Ca$^{2+}$, leading to upregulation of SK channels, postshock APD shortening, and recurrent spontaneous VF. To date, the role of SK channels in regulating ventricular tachyarrhythmias, i.e., ventricular tachycardia (VT) or VF, has not yet been described in in vivo AMI animals. A previous study (47) has reported that AMI causes Ca$^{2+}$ influx into cardiac myocytes. Therefore, as SK channels are activated by intracellular Ca$^{2+}$, it is reasonable to speculate that SK channels in cardiac myocytes could be upregulated in AMI animals to contribute to the genesis of VT/VF.
In the present study, we determined the role of SK channels in regulating ventricular tachyarrhythmias and assessed in vivo the effect of blockade of SK channels using apamin and 6,10-diaza-3(1,3),8(1,4)-dibenzena-1,5(1,4)-diquinolinacy clo- decaphane (UCL-1684) on spontaneous ventricular tachyar-
hythmias, the inducibility of ventricular tachyarrhythmias, the ventricular effective refractory period (VERP), the VF threshold (VFT), and monophasic APD at 90% repolarization (MAPD90).

**MATERIALS AND METHODS**

**Animals.** Experiments were carried out using 84 male Sprague-Dawley rats (350–450 g). All experimental and surgical procedures were approved by the Institutional Council on Animal Care and Use of Nantong University and complied with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals.

**Surgery preparation and experimental protocols.** Animals were anesthetized with α-chloralose (70 mg/kg ip) and urethane (700 mg/kg ip). An adequate depth of anesthesia was assessed before surgery by the absence of pedal and corneal reflexes and by failure to withdraw the hindlimb in response to a pinch of the paw. Supplements equal to 10% of the initial dose were given when needed. After tracheal cannulation, rats were artificially ventilated with oxygen-enriched room air. End-tidal PCO2 was continuously monitored and maintained within normal limits (35–40 mmHg) by adjusting the ventilation rate (60–80 beats/min) and/or tidal volume (2–3 ml). A warm controller (ATC1000, WPI) was used to maintain body temperature at 37°C with monitoring through rectal temperature.

Animals were allowed to stabilize for at least 30 min after surgery, at which time pretreatments were performed by an intravenous administration of either SK channel blocker or vehicle (saline). Rats were randomized into the following nine groups: 1) low-dose (7.5 μg/kg) apamin pretreatment with AMI (L-apamin-AMI group; n = 6; 2) medium-dose (22.5 μg/kg, medium dose 1) apamin pretreatment with AMI (M1-apamin-AMI group; n = 5); 2) medium-dose (37.5 μg/kg, medium dose 2) apamin pretreatment with AMI (M2-apamin-AMI group; n = 5); 4) high-dose (75.0 μg/kg) apamin pretreatment with AMI (H-apamin-AMI group; n = 7); 5) UCL-1684 (3.0 mg/kg) pretreatment with AMI (UCL-1684-AMI group; n = 7); 6) vehicle pretreatment with sham operation (vehicle-sham control group; n = 9); 7) vehicle pretreatment with AMI (vehicle-AMI group; n = 6); 8) high-dose (75.0 μg/kg) apamin pretreatment with sham operation (H-apamin-sham group; n = 7); and 9) UCL-1684 (3.0 mg/kg) pretreatment with sham operation (UCL-1684-sham group; n = 8). In addition, the effect of the time course of AMI (20 min, 1 h, 2 h, and 3 h) on VERP and MAPD90 was determined in separate vehicle-AMI rats (n = 4).

**Induction of AMI.** After pretreatment with either SK channel blocker or vehicle, the heart was exposed through the lateral thoracotomy as previously described in rats (16, 52). Briefly, the left anterior descending coronary artery (LAD) was ligated with a 6-0 silk suture near its origin between the pulmonary outflow tract and the edge of the left atrium. AMI was confirmed by the observation that the anterior wall of the left ventricle (LV) became cyanotic and an elevated ST segment on the ECG (lead II) recording.

**In vivo electrophysiology experiments.** In vivo electrophysiological experiments were performed as described previously (4). ECG (lead II) was used to record spontaneous ventricular arrhythmias and determine electrophysiological parameters, including RR, PR, QRS, and normalized QT [corrected QT (QTc)] (34).

To determine the susceptibility to arrhythmias, programmed electrophysiological stimulation (PES) was performed by a programmable stimulator (model 5328, Medtronic). Each electrode lead (A-M System) was secured with 6-0 silk to the LV wall for stimulation and the right ventricular wall for reference. PES protocols were modified from previous studies by Nguyen et al. and others (12, 25, 39, 49). Ventricular arrhythmias were induced by a train of eight stimuli with the current intensity twice the pacing threshold (Table 1) at a basic cycle length of 120 ms (8 × S1) followed by single (S2), double (S3), and triple (S4) extrastimuli. The coupling interval of the last extra-
stimulus was decreased in 2-ms steps beginning at 80 ms and ended at the point where VERP started or terminated. Ventricular tachyarrhythmia was evoked. Ventricular tachyarrhythmia was considered noninducible when PES produced either no ventricular premature beats (VPBs) or self-terminated VPBs of <6. A ventricular tachyarrhythmia was considered nonsustained when it lasted ≤15 beats and sustained when it lasted >15 beats before terminating spontaneously. Ventricular arrhythmia scores were determined by the inducibility quotient of ventricular tachyarrhythmias as follows: 0, noninducible; 1, nonsustained tachyarrhythmias induced with three extrastimuli; 2, sustained tachyarrhythmias induced with three extra-
stimuli; 3, nonsustained tachyarrhythmias induced with two extra-stimuli; 4, sustained tachyarrhythmias induced with two extra-stimuli; 5, nonsustained tachyarrhythmias induced with one extrastimulus; 6, sustained tachyarrhythmias induced with one extrastimulus; 7, tachyarrhythmias induced during a train of eight stimuli (8 × S1) at a basic cycle length of 120 ms; and 8, heart stopped before PES. When multiple forms of tachyarrhythmias occurred in one heart, the highest score was used.

Programmed stimulation protocols for the determination of the VF threshold (VFT) were performed as previously described (44). To determine VFT, a train of constant-current pulses (100 Hz, 1 s) was applied during diastole to induce VF. Current intensity started from 1 mA, and current was then delivered in steps of 1 mA with duration of

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**Table 1. Summary of ECG parameters and pacing thresholds**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>RR, ms</th>
<th>PR, ms</th>
<th>QRS, ms</th>
<th>QTc, ms</th>
<th>Pacing Threshold, mA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle-sham control</td>
<td>9</td>
<td>155.4 ± 4.3</td>
<td>52.1 ± 1.9</td>
<td>18.9 ± 1.3</td>
<td>50.6 ± 3.9</td>
<td>0.55 ± 0.2</td>
</tr>
<tr>
<td>H-apamin-sham</td>
<td>7</td>
<td>153.2 ± 2.8</td>
<td>46.2 ± 2.4</td>
<td>19.2 ± 1.5</td>
<td>59.6 ± 4.7</td>
<td>0.48 ± 0.2</td>
</tr>
<tr>
<td>UCL-1684-sham</td>
<td>8</td>
<td>151.4 ± 5.8</td>
<td>43.7 ± 2.1</td>
<td>19.1 ± 2.2</td>
<td>56.2 ± 2.5</td>
<td>0.45 ± 0.3</td>
</tr>
<tr>
<td>Vehicle-AMI</td>
<td>6</td>
<td>178.5 ± 6.2</td>
<td>51.8 ± 3.2</td>
<td>21.1 ± 2.4</td>
<td>62.5 ± 2.9</td>
<td>0.51 ± 0.2</td>
</tr>
<tr>
<td>L-apamin-AMI</td>
<td>6</td>
<td>175.1 ± 4.6</td>
<td>52.1 ± 2.3</td>
<td>20.4 ± 1.8</td>
<td>61.6 ± 3.2</td>
<td>0.54 ± 0.3</td>
</tr>
<tr>
<td>M1-apamin-AMI</td>
<td>5</td>
<td>170.2 ± 5.2</td>
<td>50.2 ± 1.5</td>
<td>19.6 ± 2.1</td>
<td>62.1 ± 3.1</td>
<td>0.50 ± 0.4</td>
</tr>
<tr>
<td>M2-apamin-AMI</td>
<td>5</td>
<td>171.2 ± 5.6</td>
<td>52.6 ± 2.6</td>
<td>20.7 ± 1.8</td>
<td>60.5 ± 4.2</td>
<td>0.54 ± 0.5</td>
</tr>
<tr>
<td>H-apamin-AMI</td>
<td>7</td>
<td>172.4 ± 6.3</td>
<td>50.8 ± 2.7</td>
<td>21.8 ± 2.6</td>
<td>61.9 ± 3.6</td>
<td>0.50 ± 0.4</td>
</tr>
<tr>
<td>UCL-1684-AMI</td>
<td>7</td>
<td>174.7 ± 6.9</td>
<td>51.9 ± 2.5</td>
<td>20.4 ± 1.7</td>
<td>64.4 ± 4.6</td>
<td>0.52 ± 0.3</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, number of rat/group. Rats were randomized into the following groups: 1) low-dose (7.5 μg/kg) apamin pretreatment with acute myocardial infarction (AMI; L-apamin-AMI group), 2) medium-dose (22.5 μg/kg) apamin pretreatment with AMI (M1-apamin-AMI group), 3) medium-dose (37.5 μg/kg) apamin pretreatment with AMI (M2-apamin-AMI group), 4) high-dose (75.0 μg/kg) apamin pretreatment with AMI (H-apamin-AMI group), 5) UCL-1684 (3.0 mg/kg) pretreatment with AMI (UCL-1684-AMI group), 6) vehicle pretreatment with sham operation (vehicle-sham control group), 7) vehicle pretreatment with AMI (vehicle-AMI group), 8) high-dose (75.0 μg/kg) apamin pretreatment with sham operation (H-apamin-sham group), and 9) UCL-1684 (3.0 mg/kg) pretreatment with sham operation (UCL-1684-sham group). QTc, normalized QT interval by RR.

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1,000 ms until VF was evoked. VFT was defined as the smallest interval that failed to evoke ventricular depolarization.

To determine VERP, a train of stimuli with the current intensity two times the pacing threshold was performed. After a train of eight stimuli at 120-ms drive cycle length (S1), a single extrastimulus (S2) was used to achieve VERP. Stimulation of the coupling interval between the last S1 and S2 stimuli (S1S2) started at 90 ms in 5-ms steps and stopped once VERP was achieved. VERP was defined as the longest S1S2 interval that failed to evoke ventricular depolarization.

The monophasic action potentials were recorded from two locations in the LV (21, 49). For monophasic action potential recordings of the MI area, the electrode was penetrated into the epicardium of the LV wall supplied by the LAD. For monophasic action potential recordings of the non-MI (NMI) area, the recording electrode was penetrated into the region between the left atrium and the site of ligation. Both of these electrodes were gradually positioned until a gentle but stable contact pressure was achieved. Reference electrodes were placed on the left chest wall. Recordings were carried out using the Powerlab 8/30 Analysis System (AD Instruments). Monophasic action potentials were amplified, band-pass filtered, and digitized by a dual bioamplifier (AD Instruments) before they were extracted and analyzed. Recordings were accepted if they had a stable baseline, a rapid upstroke phase with consistent amplitude, a smooth repolarization phase, and a stable duration. MAPD50 was defined as the monophasic action potential interval from the onset of zero-phase depolarization to the 90% repolarization level.

Analysis of AMI and measurements of the infarct area. The myocardial infarct size and area at risk (AAR) were determined as previously described (41). Upon completion of the electrophysiology experiments, Evans blue dye (10%) was retrograde perfused from the aorta. The heart was then excised, and LVs were dissected and cut into eight transverse slices of 1 mm thickness. All slices were incubated for 15 min at 37°C in a phosphate-buffered 2% 2,3,5-triphenyltetrazolium chloride solution (2 g/100 ml), fixed overnight in 10% formalin, weighed, and digitally photographed. The photographs were then analyzed with picture analysis software (ImageJ software, version 1.41, NIH). The areas in blue (nonoccluded coronary perfusion area, normal zone), red (occluded coronary perfusion area, indicating the AAR for infarction), and white (infarcted area) were quantified by an investigator blinded to the treatment protocol. All parameters were calculated by adding the eight slices together for each rat.

LV SK channel protein. Western blot measurements. Western blot measurements for SK1–SK3 channel protein were performed as previously described (18). Briefly, hearts from adult male rats (n = 5 for the vehicle-sham control group and n = 5 for the vehicle-AMI group) were removed and quickly frozen on dry ice. Frozen noninfarcted LV tissue (100 mg) was homogenized in 400 μl of buffer (50 mM Tris base, 1.0 mM EDTA, 150 mM NaCl, 0.1% SDS, 1% Triton X-100, 1% sodium deoxycholate, and 1 mM PMSF, pH 7.4, Sigma) complete with protease inhibitors (0.1 mM leupeptin and 0.3 mM PMSF, Sigma) and stirred for 30 min at 4°C. A centrifugal spin with complete with protease inhibitors (0.1 mM leupeptin and 0.3 mM PMSF, pH 7.4, Sigma) was used to achieve VERP. Stimulation of the coupling interval between the last S1 and S2 stimuli (S1S2) started at 90 ms in 5-ms steps and stopped once VERP was achieved. VERP was defined as the longest S1S2 interval that failed to evoke ventricular depolarization.

Data analysis. All values in the text and figures are expressed as means ± SE. Mean values of data from different treatment groups were compared using one-way ANOVA. For analyses that yielded a significant interaction, pairwise comparisons were made using Newman-Keuls post hoc tests (GraphPad Prism, version 5.0). Episodes of sustained VT (SVT)/VF were compared using Wilcoxon nonparametric statistical analysis. Differences were considered statistically significant at P values of <0.05.

RESULTS

Histological analysis and comparison of infarct size. A total of 84 rats were assigned to the sham control and AMI experiments. There were no significant differences in body weight and LV weight among all groups (Table 2). Histological examination and analysis of heart sections showed that both infarct area and AAR in the vehicle-AMI group was significantly (P < 0.05) different from the vehicle-sham control group (Table 2). However, pretreatment with SK channel blocker using either apamin or UCL-1684 had no significant effect on the infarct size of the LV from vehicle-AMI rats.

Comparison of spontaneous malignant ventricular tachyarrhythmias. Data from ECG recordings are shown in Table 1. There were no significant statistical differences (P > 0.05) in RR, PR, QRS, or QTc (34) among all groups. It should be noted that QTc tended to increase after AMI, but it did not reach a significant statistical difference compared with the vehicle-sham control group. Pretreatment with SK channel blocker using either apamin or UCL-1684 had no significant effect on QTc in rats with AMI.

After LAD ligation, ECG recordings continued for ~10 min to monitor spontaneous malignant ventricular arrhythmias, i.e., SVT or VF. Figure 1 shows representative traces of the ECG (II lead) recorded for ~10 min from sham control and AMI animals in the presence and absence of SK channel blocker. In a sham rat (Fig. 1A), neither SVT nor VF was observed (0 of 9 rats) except for a few VPBs (arrows) during the ~10-min ECG recording. Similarly, pretreatment with SK channel blocker using either high-dose apamin (Fig. 1B) or UCL-1684 (Fig. 1C) did not reveal any spontaneous malignant ventricular arrhythmias during the ECG recordings (0 of 7 rats in the...
H-apamin-sham group and 0 of 8 rats in the UCL-1684-sham group). In the vehicle-AMI group, four of seven rats (57%) showed VF and seven of seven rats (100%) showed SVT. Among these seven vehicle-AMI animals, one rat died from VF during the ~10-min ECG recording of spontaneous malignant ventricular arrhythmias. Figure 1D shows representative traces of the ECG recording in an AMI rat. It should be noted that a SVT occurred after ligation of the LAD, which was followed by VF. The VF lasted for 11 s and terminated automatically. All malignant ventricular arrhythmias terminated within ~3 min automatically except in one rat that died from VF in the vehicle-AMI group. In the L-apamin-AMI group, two of six rats (33%) and six of six rats (100%) showed VF and SVT, respectively. In the M1-apamin-AMI group, one of five rats (20%) and five of five rats (100%) showed VF and SVT, respectively. In the M2-apamin-AMI group, two of five rats (40%) and five of five rats (100%) showed VF and SVT, respectively. In the H-apamin-AMI group, one of seven rats (14%) and two of seven rats (28%) showed VF and SVT, respectively. Figure 1E shows representative traces during PES (100 Hz, 1 s). To determine whether VFT is altered in AMI rats and to evaluate regulation by SK channels, VFT was compared in both sham control and AMI rats in the absence and presence of pretreatment of SK channel blockers. Pretreatment with SK channel blocker using apamin or UCL-1684 significantly reduced the inducibility quotient of ventricular tachyarrhythmias (P < 0.05; Fig. 2G). Figure 2F shows representative traces of S1/S2 stimulation in a UCL-1684-AMI rat. Note that nonsustained tachyarrhythmia (top trace) was induced with one S1 stimulation and one extrastimulus (3 s) and that this nonsustained tachyarrhythmia terminated automatically within 1 s (bottom trace). In addition, pretreatment with nonpeptide SK channel blocker using apamin or UCL-1684 significantly reduced the inducibility quotient of ventricular tachyarrhythmias as evaluated by the inducibility quotient (P < 0.05; see MATERIALS AND METHODS) and apamin showed an inhibitory effect on the inducibility quotient in a dose-dependent manner.

Comparison of VFT. To determine whether VFT is altered in AMI rats and to evaluate regulation by SK channels, VFT was compared in both sham control and AMI rats in the absence and presence of pretreatment of SK channel blocker. Pretreatment with SK channel blocker using apamin or UCL-1684 significantly reduced the inducibility quotient of ventricular tachyarrhythmias as evaluated by the inducibility quotient (P < 0.05; see MATERIALS AND METHODS) and apamin showed an inhibitory effect on the inducibility quotient in a dose-dependent manner.

### Table 2. Body weights, LV weights, and comparison of infarct sizes by AMI

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Body Weight, g</th>
<th>LV Weight, g</th>
<th>AAR, g</th>
<th>IA, g</th>
<th>IA/LV, %</th>
<th>AAR/LV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle-sham control</td>
<td>9</td>
<td>392 ± 11</td>
<td>0.56 ± 0.10</td>
<td>0.05 ± 0.02</td>
<td>0</td>
<td>0</td>
<td>8.5 ± 2.2</td>
</tr>
<tr>
<td>H-apamin-sham</td>
<td>7</td>
<td>412 ± 35</td>
<td>0.53 ± 0.06</td>
<td>0.06 ± 0.02</td>
<td>0</td>
<td>0</td>
<td>9.1 ± 3.1</td>
</tr>
<tr>
<td>UCL-1684-sham</td>
<td>8</td>
<td>415 ± 22</td>
<td>0.61 ± 0.09</td>
<td>0.05 ± 0.03</td>
<td>0</td>
<td>0</td>
<td>7.8 ± 3.4</td>
</tr>
<tr>
<td>Vehicle-AMI</td>
<td>6</td>
<td>408 ± 11</td>
<td>0.52 ± 0.06</td>
<td>0.12 ± 0.10*</td>
<td>0.02 ± 0.02*</td>
<td>12.5 ± 3.9*</td>
<td>25.5 ± 3.9*</td>
</tr>
<tr>
<td>L-apamin-AMI</td>
<td>6</td>
<td>411 ± 29</td>
<td>0.63 ± 0.07</td>
<td>0.15 ± 0.08*</td>
<td>0.04 ± 0.03*</td>
<td>13.7 ± 4.5*</td>
<td>23.8 ± 3.6*</td>
</tr>
<tr>
<td>M1-apamin-AMI</td>
<td>5</td>
<td>414 ± 20</td>
<td>0.57 ± 0.08</td>
<td>0.13 ± 0.03*</td>
<td>0.04 ± 0.04*</td>
<td>10.7 ± 5.4*</td>
<td>21.9 ± 4.7*</td>
</tr>
<tr>
<td>M2-apamin-AMI</td>
<td>5</td>
<td>413 ± 25</td>
<td>0.61 ± 0.05</td>
<td>0.15 ± 0.10*</td>
<td>0.05 ± 0.04*</td>
<td>11.5 ± 4.7*</td>
<td>22.8 ± 3.8*</td>
</tr>
<tr>
<td>H-apamin-AMI</td>
<td>7</td>
<td>406 ± 12</td>
<td>0.53 ± 0.10</td>
<td>0.12 ± 0.05*</td>
<td>0.02 ± 0.02*</td>
<td>12.5 ± 4.1*</td>
<td>23.4 ± 4.2*</td>
</tr>
<tr>
<td>UCL-1684-AMI</td>
<td>7</td>
<td>397 ± 22</td>
<td>0.59 ± 0.12</td>
<td>0.16 ± 0.10*</td>
<td>0.03 ± 0.02*</td>
<td>11.2 ± 4.7*</td>
<td>26.8 ± 4.8*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, number of rats/group. LV, left ventricular; AAR, area at risk; IA, infarct area. *P < 0.05 vs. the vehicle-sham control group (by one-way ANOVA).

Comparison of inducibility of ventricular arrhythmias. To evaluate the effect of SK channel blocker on the inducibility of ventricular arrhythmias, responses were compared in the absence and presence of the SK channel blockers apamin or UCL-1684 in AMI animals. Figure 2D shows representative traces of a train of S1 stimulation in a vehicle-AMI rat. Note that VF was induced by the train of S1 stimuli (8 × S1) and that the VF was terminated automatically ~18 s after the stop of S1 stimulation (score: 7). Figure 2E shows representative traces of S1/S2/S3 stimulation in a H-apamin-AMI rat. Note that nonsustained tachyarrhythmia (top trace) was induced by a train of S1 stimulation and two extrastimuli (score: 3) and that this nonsustained tachyarrhythmia terminated automatically within 1 s (bottom trace). In addition, pretreatment with nonpeptide SK channel blocker using apamin or UCL-1684 also significantly reduced the inducibility quotient of ventricular tachyarrhythmias (P < 0.05; Fig. 2G). Figure 2F shows representative traces of S1/S2 stimulation in a UCL-1684-AMI rat. Note that nonsustained tachyarrhythmia (top trace) was induced with one extrastimulus (score: 5) and that this nonsustained tachyarrhythmia terminated automatically within 1 s (bottom trace, score: 3). Figure 2G shows a summary comparing the inducibility of ventricular tachyarrhythmias in sham-operated control and AMI animals in the absence and presence of SK channel blockers. Pretreatment with SK channel blocker using apamin or UCL-1684 significantly reduced the inducibility quotient of ventricular tachyarrhythmias as evaluated by the inducibility quotient (P < 0.05; see MATERIALS AND METHODS) and apamin showed an inhibitory effect on the inducibility quotient in a dose-dependent manner.

Comparison of VFT. To determine whether VFT is altered in AMI rats and to evaluate regulation by SK channels, VFT was compared in both sham control and AMI rats in the absence and presence of pretreatment of SK channel blocker. Pretreatment with SK channel blocker using apamin or UCL-1684 significantly reduced the inducibility quotient of ventricular tachyarrhythmias as evaluated by the inducibility quotient (P < 0.05; see MATERIALS AND METHODS) and apamin showed an inhibitory effect on the inducibility quotient in a dose-dependent manner.
Fig. 1. Effect of blockade of small-conductance (SK) channels on spontaneous malignant ventricular arrhythmias in rats with acute myocardial infarction (AMI). Rats were randomized into the following groups: 1) low-dose (7.5 μg/kg) apamin pretreatment with AMI (L-apamin-AMI group), 2) medium-dose (22.5 μg/kg) apamin pretreatment with AMI (M1-apamin-AMI group), 3) medium-dose (37.5 μg/kg) apamin pretreatment with AMI (M2-apamin-AMI group), 4) high-dose (75.0 μg/kg) apamin pretreatment with AMI (H-apamin-AMI group), 5) UCL-1684 (3.0 mg/kg) pretreatment with AMI (UCL-1684-AMI group), 6) vehicle pretreatment with sham operation (vehicle-sham control group), 7) vehicle pretreatment with AMI (vehicle-AMI group), 8) high-dose (75.0 μg/kg) apamin pretreatment with sham operation (H-apamin-sham group), and 9) UCL-1684 (3.0 mg/kg) pretreatment with sham operation (UCL-1684-sham group).

A: representative traces of an ECG (lead II) recording in a sham-operated rat. Neither sustained ventricular tachycardia (SVT) nor ventricular fibrillation (VF) was observed except for a few ventricular premature beats (VPBs; arrows) during the 10-min ECG recording after the sham operation. B and C: pretreatment with SK channel blocker using either high-dose apamin (B) or UCL-1684 (C) did not reveal any malignant ventricular arrhythmias except for a few VPBs (arrows) during the 10-min ECG recordings. D: representative traces of ECG recording in an AMI rat. A SVT occurred ~3 s after AMI, which followed by a VF. The VF lasted for 11 s and terminated spontaneously. E: representative traces of ECG recording in an AMI rat with high-dose apamin pretreatment. A SVT occurred ~1 min after AMI. The SVT lasted for ~2 s and terminated spontaneously. F: representative traces of ECG recording in an AMI rat with UCL-1684 pretreatment. No spontaneous malignant ventricular arrhythmias occurred except for a spontaneous non-SVT and a few VPBs (arrows) during the ECG recordings. G: summary data showing the inhibitory effects of SK channel blocker on the duration of spontaneous SVT/VF (left) and average numbers of episodes of spontaneous SVT/VF (right) in AMI rats. Pretreatment with the SK channel blocker apamin significantly inhibited both the duration of SVT/VF and episodes of spontaneous SVT/VF in AMI animals in a dose-dependent manner. UCL-1684 had a similarly inhibitory effect as high-dose apamin on spontaneous malignant ventricular arrhythmias in AMI animals. *p < 0.05 vs. the vehicle-AMI group; †p < 0.05 vs. the L-apamin-AMI group.
was increased up to 10 mA (Fig. 3C, right). Figure 3D, left, shows representative traces when the stimulus intensity was 1 mA in a vehicle-AMI rat. VF was able to be evoked until 2 mA of current intensity was reached (Fig. 3D, right). Figure 3E, left, shows representative traces when the stimulus intensity was 1 mA in an AMI rat pretreated with a high dose of apamin. VF was able to be evoked until 5 mA of current intensity was reached (Fig. 3E, right). Figure 3G shows summary data of the effect of SK channel blockers on VFT. VFT was significantly reduced in AMI rats (2.5 ± 0.76 mA, n = 6) compared with sham animals (10.4 ± 0.56 mA, n = 9) without pretreatment with SK channel blocker (P < 0.05). Pretreatment with a low dose of apamin (2.8 ± 0.48 mA, n = 6) did not significantly change VFT in AMI rats (P > 0.05). In contrast, pretreatment with medium dose 1 (6.0 ± 1.41 mA, n = 5), medium dose 2 (6.7 ± 0.87 mA, n = 5), or a high dose (6.7 ± 0.87 mA, n = 7) of apamin as well as with UCL-1684 (7.1 ± 0.77 mA, n = 7) significantly elevated VFT in AMI animals (P < 0.05). Both high-dose apamin (9.3 ± 0.34 mA, n = 7) and UCL-1684 (9.4 ± 0.40 mA, n = 8) failed to change VFT in sham animals (P > 0.05).

Comparison of VERP. To determine whether VERP is altered in AMI rats and to evaluate regulation by SK channels,
VERP was compared among groups. Figure 4A shows representative ECG traces for VERP from a vehicle-sham control animal. The programmed stimulus with 90 ms of S1S2 interval could not induce VERP, i.e., ventricular depolarization followed by S2 stimulation (Fig. 4A, left, arrows). However, the programmed stimuli successfully evoked VERP, with an absence of ventricular depolarization followed by S2 stimulation (arrows), when the S1S2 interval was 50 ms (Fig. 4A, right). Similarly, the S1S2 programmed stimuli successfully evoked VERP when the S1S2 interval was reduced to 45 ms from 90 ms in an apamin-sham rat (Fig. 4B) and to 50 ms from 90 ms in a UCL-1684-sham rat (Fig. 4C). Figure 4D shows representative ECG traces for VERP from a vehicle-AMI animal. The programmed stimuli successfully evoked VERP when the S1S2 interval was reduced to 35 ms from 90 ms. Figure 4E shows representative ECG traces for VERP from an H-apamin-AMI animal. The programmed stimuli successfully evoked VERP when the S1S2 interval was reduced to 50 ms from 90 ms. Figure 4F shows representative ECG traces for VERP from an UCL-1684-AMI animal. The programmed stimuli successfully evoked VERP when the S1S2 interval was reduced to 55 ms from 90 ms. Figure 4G shows summary data. The VERP in AMI rats (37.5 ± 3.2 ms, n = 6) was significantly reduced compared with that in sham control rats (52.5 ± 3.2 ms, n = 9, P < 0.05). Pretreatment with a low dose of apamin did not significantly increase VERP in AMI animals. Pretreatment with either a higher dose of apamin or UCL-1684 (48.0 ± 3.0 ms for the

**Fig. 3.** VF threshold (VFT) determined by a train of stimuli (100 Hz, 1 s) started from 1 mA of current intensity and stopped until VF occurred in sham control and AMI rats. A: VF was able to be evoked until the current intensity reached 10 mA (right) in a vehicle-sham rat. B: VF was able to be evoked until the current intensity reached 9 mA (right) in a H-apamin-sham rat. C: VF was able to be evoked until the current intensity reached 10 mA (right) in a UCL-1684-sham rat. D: VF was able to be evoked by a train of stimuli with only 2 mA (right) in a vehicle-AMI rat. Note that AMI obviously reduced VFT compared with that in sham control rat (A). E: VF was able to be evoked by a train of stimuli with 7 mA (right) in a H-apamin-AMI rat. F: VF was able to be evoked by a train of stimuli with 5 mA (right) in an UCL-1684-AMI rat. Note that VFT was able to be elevated in the presence of SK channel blocker in AMI animals. G: summary data showing that VFT was significantly reduced in AMI rats compared with sham control rats. Pretreatment with high-dose apamin did not significantly change VFT in sham control rats. However, pretreatment with SK channel blocker using either high-dose apamin or UCL-1684 significantly increased VFT in vehicle-AMI animals.

*P < 0.05 vs. the vehicle-sham control group; #P < 0.05 vs. the vehicle-AMI group.
M1-apamin-AMI group, \(n = 5\); 49.0 ± 3.3 ms for the M2-apamin-AMI group, \(n = 5\); 50 ± 3.5 ms for the H-apamin-AMI group, \(n = 7\); and 52 ± 4.6 ms for the UCL-1684-AMI group, \(n = 7\)). Significantly (\(P < 0.05\)) increased VERP in AMI animals in a dose-dependent manner. In contrast, pretreatment with either apamin or UCL-1684 failed (\(P > 0.05\)) to increase VERP in sham control animals (45 ± 2.9 ms for the H-apamin-sham group, \(n = 7\); and 42 ± 5.0 ms for the UCL-1684-sham group, \(n = 8\)). Additionally, the effect of the time course of AMI (20 min, 1 h, 2 h, and 3 h after occlusion of the LAD) on VERP was determined in a separate group of animals (\(n = 4\)). There were no significant differences in VERP at the different time points (data not shown). These data indicate that the shortening of VERP mediated by AMI is time independent during 3 h of observation.

**Comparison of MAPD\(_{90}\).** Based on the available evidence, MAPD\(_{90}\) shortening could be a mechanism underlying VF (50) by promoting late phase 3 early afterdepolarizations (7) or by inducing transmural heterogeneity of repolarization (3). Recently, it has been reported that monophasic action potential shortening was involved in the recurrent spontaneous VT/VF in the failing heart (3).

To determine whether MAPD\(_{90}\) is altered in AMI rats and to evaluate regulation by SK channels, MAPD\(_{90}\) were compared between sham control and AMI rats with or without pretreatment with SK channel blocker. Figure 5A shows representative monophasic action potential traces recorded from the epicardium of the LV wall supplied by the LAD in a vehicle-sham (left trace), H-apamin-sham (middle trace), and UCL-1684-sham (right trace) rat, respectively. MAPD\(_{90}\) averaged 59.4 ±
Fig. 5. Effect of SK channel blocker on monophasic action potential (MAP) duration at 90% repolarization (MAPD90) in sham control and AMI rats. 

A: representative MAP traces recorded from the left ventricle in a vehicle-sham rat (left trace), a H-apamin-sham rat (middle trace), and a UCL-1684-sham rat (right trace), respectively. B: representative MAP traces recorded from the non-myocardial infarcted (NMI) area in a vehicle-AMI rat (left trace), a H-apamin-AMI rat (middle trace), and a UCL-1684-AMI rat (right trace), respectively. Pretreatment with SK channel blocker using either high-dose apamin or UCL-1684 failed to change the width of MAP recorded from the NMI area. C: representative MAP traces recorded from the myocardial infarcted (MI) area in AMI rats. Note that AMI obviously shortened the width of MAP (left trace) compared with that recorded from either the NMI area (B, left trace) or the left ventricle in a vehicle-sham control rat (A, left trace). Pretreatment with SK channel blocker using either high-dose apamin (middle trace) or UCL-1684 (right trace) obviously prolonged the shortened MAPD90 caused by AMI (left trace). 

D: summary data showing that MAPD90 recorded from the left ventricle in sham control animals was not significantly different from animals pretreated with SK channel blocker using either high-dose apamin or UCL-1684. Similarly, there were no significant statistical differences in MAPD90 recorded from the NMI area among the vehicle-AMI, H-apamin-AMI, and UCL1684-AMI groups. MAPD90 recorded from the MI area in AMI rats was significantly shortened compared with that recorded from either the left ventricle in vehicle-sham control rats or from the NMI area in AMI rats. Pretreatment with SK channel blocker using either apamin or UCL-1684 significantly prolonged MAPD90 recorded from the MI area in AMI animals. MAPD90 was defined as the MAP duration from the onset of zero-phase depolarization to the 90% repolarization level. *P < 0.05 vs. the vehicle-sham control group; †P < 0.05 vs. the NMI area in the vehicle-AMI group; #P < 0.05 vs. the MI area in the vehicle-AMI group.

The figure shows representative MAP traces recorded from the left ventricle in sham control and AMI rats. The MAPD90 was significantly increased in the MI area compared to the NMI area in AMI rats. Pretreatment with SK channel blocker using either high-dose apamin or UCL-1684 significantly prolonged the MAPD90 recorded from the MI area in AMI animals. The MAPD90 was not significantly different from the vehicle-sham control group. The diagram also shows the summary data of MAPD90 recorded from the NMI area among the vehicle-AMI, H-apamin-AMI, and UCL1684-AMI groups, with no significant statistical differences observed. The MI area in AMI rats showed significantly shortened MAPD90 compared to the NMI area in AMI rats. Pretreatment with SK channel blocker using either apamin or UCL-1684 significantly prolonged the MAPD90 recorded from the MI area in AMI animals.
vehicle-AMI rats ($P < 0.05$). Pretreatment with SK channel blocker using either high-dose apamin ($56.2 \pm 3.4$ ms, $n = 7$) or UCL-1684 ($54.0 \pm 2.9$, $n = 7$) significantly prolonged \(\text{MAPD}_{90} (P < 0.05)\) compared with that recorded from the MI area in the vehicle-AMI group (Fig. 5D).

The effect of the time course of AMI (20 min, 1 h, 2 h, and 3 h after occlusion of the LAD) on \(\text{MAPD}_{90}\) was determined in a separate group of animals ($n = 4$). There were no significant differences in \(\text{MAPD}_{90}\) recorded from the MI or NMI area at the different time points (data not shown). These data indicate that the shortening of \(\text{MAPD}_{90}\) recorded from the MI area after AMI is time independent during 3 h of observation.

**Comparison of SK channel gene (Kcnn1–Kcnn3) and protein expression.** It has been reported that SK channels are expressed in the rat heart (51) and that the density of SK currents in epicardial cardiac myocytes is increased in the failing ventricle (11). Therefore, we compared the gene and protein expression of SK1–SK3 channels in LVs between sham control animals ($n = 5$ for RT-PCR and $n = 5$ for Western blot analysis) and AMI animals ($n = 5$ for RT-PCR and $n = 5$ for Western blot analysis). No significant statistical differences in SK1–SK3 expression between sham control and AMI rats were detected (Fig. 6, $A$ and $B$ for RT-PCR and $C$ and $D$ for Western blot analysis).

**DISCUSSION**

A recent in vitro study (11) reported that blockade of SK channels with apamin reduced APD shortening and spontaneous VF induced by postpacing or postshock in a tachycardia-induced heart failure model. Additionally, this same study (11) reported that the density of SK currents in epicardial cardiac myocytes was increased in failing ventricles. These findings indicate that activation or upregulation of SK channels may contribute to the mechanisms of VF in heart failure. To date, whether activation or upregulation of SK channels involves VF has not yet been determined in vivo in AMI. The present study found that spontaneous malignant ventricular tachyarrhythmias, i.e., SVT and VF, was increased, the inducibility of ventricular tachyarrhythmias was elevated, and VERP was shortened in AMI rats compared with sham control rats. Pretreatment in the AMI group with the SK channel blockers apamin or UCL-1684 significantly inhibited SVT/VF, reduced the inducibility of ventricular tachyarrhythmias, and prolonged

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**Fig. 6. Expression of SK1–SK3 channels in left ventricles.** $A$: RT-PCR analysis showing the mRNA expression of SK1–SK3 channels between the sham control and AMI groups. $B$: summary data showing that there were no significant statistical differences in the mRNA expression of SK1–SK3 channels between the sham control ($n = 5$) and AMI ($n = 5$) groups. $C$: Western blot analysis showing the protein expression of SK1–SK3 channels between the sham control and AMI groups. $D$: summary data showing that there were no significant statistical differences in the protein expression of SK1–SK3 channels between the sham control ($n = 5$) and AMI ($n = 5$) groups. All values were normalized to the value of GAPDH.
VERP. Additionally, VFT was reduced and inhibition of SK channels elevated VFT in AMI animals. Finally, epicardial electrophysiological recordings showed that MAPD_{90} in the MI area was shortened and that inhibition of SK channels in AMI rats significantly prolonged MAPD_{90} in the MI area.

In the present study, we used reliable PES protocols to compare ventricular vulnerability by scoring ventricular tachyarrhythmias. This method has been well accepted and published to evaluate the inducibility of ventricular arrhythmias in AMI (12, 39). VFT is defined as the smallest amount of current required to elicit VF (2, 44), and it has been widely used to test the efficacy of antiarrhythmic agents and to establish safety guidelines for medical treatment (2). Both the scoring of ventricular tachyarrhythmias elicited by PES and VFT represent the susceptibility to ventricular tachyarrhythmias. We found that the inducibility quotient of ventricular tachyarrhythmias was increased and VFT was reduced in AMI rats, which are consistent with previous reports (25, 49). Mechanisms that contribute to the differences in the inducibility of ventricular tachyarrhythmias and VFT between AMI and sham control animals are not presently known. Extracellular K^{+} accumulation seems to be responsible for the depolarization of the tissue that surrounds the ischemic region, which creates an injury current between ischemic and normal cells that could initiate ventricular tachyarrhythmias (5). K^{+} efflux induces a reduction in APD in the ischemic region that is more pronounced in epicardial tissue (17). As a result, an inhomogeneity of APD and refractory period occurs within the same ischemic region, leading to the development of reentrant circuits (45). Increasing the refractory dispersion state intensifies repolarization inhomogeneity, which increased the inducibility of ventricular tachyarrhythmias and reduces VFT (13). This is in fact supported by our findings that MAPD_{90} was shortened in the MI area without an alteration in MAPD_{90} in the NMI area in AMI animals and that inhibition of SK channels significantly prolonged MAPD_{90} in the MI area (Fig. 5).

VERP in the intact heart is the result of a complex series of events and is only an approximation of the ventricular repolarization duration determined from individual cells. Studies (21, 37) have shown that VERP is shortened by transmural ischemia after coronary artery occlusion, which was confirmed in this study by showing that VERP was reduced in rats with AMI. An increase in extracellular K^{+} caused by ischemia in the myocardial cell in combination with hypoxia and local acidosis may contribute to the reduction of VERP (27).

Combined with our findings showing that inhibition of SK channels reduced the inducibility quotient of ventricular arrhythmias, elevated VFT, and prolonged VERP in the MI area in AMI rats, we expect that activation of SK channels increases the K^{+} efflux from the LV epicardium to elevate extracellular K^{+} in cardiac myocytes. Thus, activation of SK channels would be expected to contribute to the elevated inducibility of VF in AMI rats. Obviously, future studies are needed to confirm these possibilities and identify the cellular mechanisms responsible for the activation of SK channels in AMI animals. MAPD_{90} represents the time course of repolarization in local cardiac myocytes (35, 38, 43). Massive intracellular K^{+} efflux has been considered responsible for reduced MAPD_{90} (20, 50). Our data showed that MAPD_{90} was shortened in the MI area in AMI rats, which is consistent with a previous study (21). It has been reported that ventricular arrhythmias could be caused by early afterdepolarizations that arise from current flowing through L-type Ca^{2+} channels and high-frequency Ca^{2+} sparks from the sarcoplasmic reticulum evoked by a Ca^{2+}-overloaded sarcoplasmic reticulum (48). Therefore, an increase in intracellular Ca^{2+} would be expected to activate SK Ca^{2+}-dependent channels of cardiac myocytes in AMI animals. SK channels mainly contribute to the medium afterhyperpolarization potential after action potentials to regulate the firing rate of neurons (1). Whether SK channels contribute to the repolarization phase to control APD is not yet fully understood. We (6) have reported that bath application of apamin broadens action potentials in the hippocampus dentate gyrus. Recently, we examined the effect of blockade of SK channels on repolarization in parasympathetic cardiac motor neurons in the nucleus ambiguous. We found that application of either apamin or UCL-1684 to parasympathetic cardiac motor neurons significantly increased the spike half-width of single action potentials (30). It has also been reported that SK channels are expressed in cardiac myocytes of the LV and regulate the repolarization phase of cardiac action potentials in the mouse (9, 51). These findings support a role for SK channels in regulating the repolarization phase to control MAPD_{90} in AMI animals. Together with evidence showing that shortening of monophasic action potentials is one of the causes of reentry and trigger that lead to VF (23), our findings indicate that activation of SK channels may underlie the mechanisms of spontaneous SVT/VF and inducibility of ventricular tachyarrhythmias induced by AMI. Our data showed that inhibition of SK channels reduces the shortening of MAPD_{90} in the MI area and reduces the repolarization dispersion, which may contribute to decreased reentry and the inhibitory effect on spontaneous ventricular arrhythmias and inducibility of tachyarrhythmias in AMI.

The alteration of SK channels involved in SVT/VF from AMI animals could also be explained by a change in the autonomic nerve system. It has been reported that in AMI patients, VF is the most common lethal arrhythmia and is preceded by signs of sympathetic overactivity (40). In animals with AMI, cardiac sympathetic nerve activity was increased (32), which is important in the genesis of VF (24). Recently, we (8, 18) reported that inhibition of SK channels in the hypothalamic paraventricular nucleus (PVN) increased the excitability of PVN neurons and sympathetic nerve activity. These findings indicate that inhibition of SK channels among presympathetic PVN neurons may increase the sympathetic outflow, which is expected to involve the genesis of VF during AMI. However, it is not the case in the present study, as blockade of SK channels involves the inhibition of VF in AMI rats. Due to the fact that SK channels are expressed in both presympathetic PVN neurons in the hypothalamus and parasympathetic cardiac motor neurons in the nucleus ambiguous (30, 31), in addition to the importance that these autonomic neurons play in regulating sympathetic and vagal nerve activity, future studies are warranted to determine the central neuronal mechanisms of activation of SK channels involved in ventricular arrhythmias in AMI.

Further examination of SK1–SK3 channels in the LV showed that although the expression of these channels (mRNA and protein) was not altered in AMI rats, inhibition of SK channels did induce a protective effect on spontaneous SVT/VF and the inducibility of ventricular tachyarrhythmias.
and reversed the shorting of MAPD90. This finding suggests that the LV from AMI rats displays an activation of SK channel function.

In summary, our data support an important functional role of SK channels in regulating cardiac ventricular arrhythmias. Activation of SK channels involves the genesis of both spontaneous SVT/VF and electrical ventricular instability in AMI rats. Inhibition of SK channels reduces the shortening of MAPD90 in the MI area, which may contribute to the inhibitory effect on spontaneous ventricular tachyarrhythmias and susceptibility to arrhythmia in AMI rats. We speculate that inhibition of SK channels may be an important approach in preventing and treating ventricular arrhythmias in AMI. Future studies are needed to fully determine the mechanisms that contribute to SK channel activation in the pathogenesis of AMI.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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