Prior ischemia enhances arrhythmogenicity in isolated canine ventricular wedge model of long QT 3

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Abstract

Objective: Ventricular tachyarrhythmias (VTs) occur frequently in patients having long QT syndrome (LQTS) or after acute myocardial ischemia. However, the synergistic effects of ischemia and LQTS on arrhythmia development are unclear. We evaluated the contribution of a prior episode of ischemia on the arrhythmogenicity of the LQTS. Methods: Using a 256-channel optical mapping system, we mapped action potentials on the cut-exposed transmural surfaces of perfused and preconditioned muscle wedges isolated from canine left ventricular walls and recorded their transmural electrocardiogram (ECG). Results: We observed that 40 min of global ischemia followed by 60 min of reperfusion, at which time action potential duration (APD) and conduction velocity had recovered, significantly enhanced the APD prolongation produced by 20 nmol/l anemone toxin II (ATX-II). Wedges after the above ischemia, reperfusion, and ATX-II procedures had 100% (8/8) occurrences of early afterdepolarizations (EADs) and 87.5% (7/8) occurrences of spontaneous VTs and reentry. We observed epicardial, midmyocardial, and endocardial occurrences of EADs in one, seven, and four wedges, respectively. Focal EADs and reentry were responsible for 73% and 18% of the repetitive activations in the VTs. In contrast, neither EADs nor VTs occurred in eight control wedges following identical procedures except without ischemia, and VT occurred in 20% wedges (2/10) after ischemia and reperfusion but before ATX-II. Conclusion: A prior episode of acute ischemia, even after apparent electrophysiologic recovery, enhances the arrhythmogenicity of LQTS induced by ATX-II through the development of EADs and reentry.

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1. Introduction

Both myocardial ischemia and long QT syndrome (LQTS) [1] contribute to ventricular tachyarrhythmias (VTs) that can degenerate to ventricular fibrillation, causing sudden cardiac death. Acute ischemia can initiate VT directly during ischemia and in the initial minutes of reperfusion and can cause oxidative damage and persistent cellular remodeling, leading to heart failure after reperfusion. Patients with LQTS have an increased probability of developing torsades de pointes (TdP) [2], possibly triggered by early afterdepolarizations (EADs) [3–6] arising from the Purkinje network [4], or ventricular muscle [3,7,8]. LQTS can be divided into multiple subtypes depending on the affected membrane ionic currents (e.g., LQT1, LQT2, and LQT3, due to decreased slow ($I_{Ks}$) and rapid ($I_{Kr}$) delayed rectifier K+ currents and to the slowed inactivation process of Na+ current, respectively). Reducing the outward currents (e.g., LQT1 and LQT2) or enhancing the inward current (e.g., LQT3) prolongs QT interval. Although the arrhythmogenicity of myocardial ischemia/reperfusion and LQTS have been well documented individually, the effects of myocardial ischemia/reperfusion in the setting of LQTS are unclear. Furthermore, the relative contributions of endocardium, midmyocardium, and epicardium to the generation of EADs, and the relative contributions of focal EADs and reentry to ventricular activation during TdP are not resolved in LQTS. The purpose of this study was to test the hypothesis that a prior episode of acute ischemia would leave persisted effects that affect the arrhythmogenicity of LQTS. We used arterially perfused wedges isolated from canine left ventricular free walls in which a model of LQT3...
was created with anemone toxin II (ATX-II), a drug that slows the inactivation of Na⁺ current.

2. Methods

The investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996). We harvested hearts from 18 adult mongrel dogs, after intravenous injections of heparin sodium (5000 units) and pentobarbital sodium (30 mg/kg body weight), and quickly (<15 s from the time of harvest) initiated cardioplegic perfusion through the aorta with an ice-cold hyperkalemia solution (Tyrode’s solution as shown below with 15 mmol/l KCl). We then isolated one transmural wedge from the left ventricular free wall of each heart, using our published procedures [9–11]. Each wedge (20–30 mm long by 4–7 mm wide on the epicardium, and 12–20 mm transmural) contained an artery (a branch of either the left anterior descending or circumflex artery with a diameter of ≥1 mm) along its length. Two plastic cannulas, one for perfusion, the other for arterial pressure monitoring, were inserted and secured into the two openings of the artery. Major leaks in the wedges were ligated with silk sutures. The isolated tissues were mounted in a warmed chamber (Radnoti, Morovia, CA) with the cut-exposed transmural observation surface up, perfused with 37 °C Tyrode’s solution (in mmol/l, NaCl 128.0, KCl 4.69, NaHCO3 22.0, NaH2PO4 0.65, MgCl2 0.50, dextrose 11.1, CaCl2 2.0, and gassed with 95% O2 –5% CO2) at an arterial pressure of 40–50 mm Hg, and immersed in the perfusion efflux. We evaluated the healthiness of tissue after >60 min of recovery using our published criteria [9–11]. We demonstrated previously [9] that wedges prepared and verified with these procedures were stable and had transmural dispersions of action potential duration (APD) and conduction velocity similar to those recorded in intact hearts [12–14].

Fig. 1 shows the experimental protocols. All wedges were treated with 5 min of pre-conditioning ischemia after being placed in the bath and perfused for >20 min, as we performed routinely [9–11]. The preconditioning served the purposes of reducing inter-tissue differences in the inevitable ischemic insults during the heart removal and wedge isolation, and of improving recovery after ischemia. There are no reported persistent effects on action potential and conduction by 5 min of preconditioning ischemia. Each wedge was stained with di-4-ANEPPS (Molecular Probes, Eugene, OR, ~4 μmol/l in perfusate), a transmembrane potential sensitive fluorescence dye, after >90 min equilibration with Tyrode’s perfusate. We suppressed muscle contraction with cytochalasin D [9,15] (Sigma, St. Louis, MO, 20–30 μmol/l in perfusate), which disrupted the cytoskeleton of myocytes, after healthiness verification. We used two groups of wedges with identical procedures except that the perfusion was stopped for 40 min in the ischemia group (10 wedges) and continued in the control group (8 wedges). We lowered the fluid level of bath during ischemia (in the ischemia group) to expose the cut-exposed transmural mapping (top) surfaces of the wedges, which were covered only by a thin layer of moisture (maintained by surface tension and restricted room air access of the chamber). Two silver electrodes were placed, one in the epicardium and the other in the endocardium of each wedge, to record the transmural electrocardiogram (ECG). Endocardial stimuli (2 ms in duration and at twice the diastolic current threshold, delivered by a bipolar electrode) paced the wedges at a cycle length (CL) of 1000 ms (default) or as specified. An optical mapping system with a 256-element (16 × 16) photodiode camera (C4675, Hamamatsu, Japan, resolution: 1.2
mm) [9] recorded the baseline data (Data 1, fluorescent APs on the transmural surface, transmural ECG, and arterial perfusion pressure, in segments of 5 or 10 s, at a rate of 1000 samples-channel$^{-1}$.s$^{-1}$) sequentially during fixed pacing CLs that were progressively lengthened from 500, 1000, 2000, to 4000 ms, after the tissue stabilization, dye staining, healthiness verification, and immobilization. Each segment of data was preceded by >20 pacing stimuli. The mapping area covered 80–100% of the transmural surfaces of the wedges. Each photodiode in our optical mapping system covered a surface area of 1.1$\times$1.1 mm. The above sequences of data recording were repeated (Data 2) after 40 min of ischemia and 60 min of reperfusion (ischemia group) or after 100 min of perfusion (control group). We then added ATX-II (Calbiochem-Novabiochem, San Diego, CA), which delays the inactivation of sodium current, to the perfusate at 20.0 nmol/l, a concentration that was used frequently to create LQT3 models [16–22], and repeated the above recording sequences 20 min later (Data 3). Data 1–3 in the ischemia and control groups are abbreviated as I1–I3 and C1–C3. We completed the protocols in eight wedges of each group, but had to terminate the ischemia protocol before adding ATX-II in two other wedges due to sustained fibrillation after the ischemia and reperfusion.

We measured APD from the interval between the maximum rate of depolarization and peak of the second-order derivative of AP, as reported previously [9,23], with visual inspection and manual correction. The epicardial, endocardial, and mid-myocardial APDs were represented by the means and standard deviations of the APDs at all recording sites along the first epicardial row, first endocardial row, and a mid-myocardial row having the longest mean APD. The mean velocity of conduction was calculated from the local velocities at all sites. EAD was identified as a depolarization or hump superimposed on the phase 3 or phase 4 of the AP. Reentry was identified as a continuous path of wave front that spontaneously returned to the region of initial activation. ANOVA and Fischer’s PLSD test were used for inter-group statistical analysis. Differences were considered significant if $p < 0.05$. Data are expressed as mean $\pm$ standard deviation.

3. Results

The wedges in both control (C) and ischemia (I) groups were similar during the baseline recording, with $\leq 3\%$ of inter-group differences in the mean velocities of conduction and in the epicardial, mid-myocardial, and endocardial mean

![Fig. 2. Epicardial, mid-myocardial, and endocardial APDs at pacing cycle lengths (CL) of 2000 and 4000 ms (panels A – B), the transmural differences of APD (mean endocardial APD – mean epicardial APD) during the baseline recording in both Groups (panel C), the occurrences of EAD and VT (panel D), and the transmural positions (as percentage of the wall thickness) of the mid-myocardial row of recording sites having the longest mean-APD (panel E). C1 – C3 and I1–I3 indicate three different data recording periods (1, 2, and 3) in Control (C) and Ischemia (I) Groups, as defined in Fig. 1. The control group has eight wedges. The ischemia group contains either eight wedges that completed the protocol (panels A – C and E) or ten wedges (panel D, including two additional wedges that had persistent VTs after $>60$ min of reperfusion). Error bars indicate standard deviations. Epi, Mid, and Endo are the epicardium, mid-myocardium, and endocardium. The '*'s above the ischemia columns indicate significant differences ($p < 0.05$) from the corresponding controls (e.g., I2 vs. C2). APDs recovered well after ischemia and reperfusion with small but clear ($p < 0.0001$) prolongation of the mean APDs (I2–C2: 5.1 ms, 11.3 ms, and 10.1 ms at CL of 2000 ms, and 8.9 ms, 8.0 ms, and 7.1 ms at CL of 4000 ms, respectively, in Epi, Mid, and Endo). Significantly ($p < 0.05$) longer APDs in the mid-myocardium than in the epicardium and endocardium (M cells) are indicated with "**".

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APDs at all pacing CLs (C1 and I1, Fig. 2). The control wedges were stable with no statistical differences in the mean velocities of conduction (0.4% reduction, \( p = 0.71 \)) and in the mean APDs (differences: <3 ms, \( p > 0.12 \)), recorded 100 min apart during continued perfusion (C1 and C2, Fig. 2). There were no statistical differences between the longest mid-myocardial and endocardial APDs before ischemia (C1, C2, and I1), although the differences between the epicardial and endocardial APDs were always significant \( (p < 0.001) \). APDs increased from the epicardium to endocardium and with the pacing CL. The baseline (C1 and I1) differences between the epicardial and endocardial APDs (Fig. 2C) were similar to the previous observations in the wedge preparation [9] and in intact hearts [12–14]. None of the wedges had EADs or VTs before ischemia (I1, C1, and C2, Fig. 2D). Therefore, the wedges in both groups were similar, healthy, stable, without excessive mid-myocardial APD prolongation during long CL [8,24], and without spontaneous EADs or VTs before ischemia (C1, I1, and C2), similar to what we have found previously [9–11].

Forty minutes of ischemia and 60 min of reperfusion (I2) produced neither spontaneous EADs nor VTs in eight wedges but spontaneous VT in two other wedges, in which the experiments were terminated before ATX-II perfusion due to sustained VT (Fig. 2D). The low incidence of arrhythmias after 60 min of reperfusion was consistent with our previous study [10] in which we observed that most reperfusion reentry occurred during the initial seconds and terminated within 19 min of reperfusion. The ischemia and reperfusion lengthened the mean APDs (I2) slightly (<12 ms from the corresponding recordings at I1 and C2, Fig. 2A–B), and slowed the mean velocities of conduction by 3.9% \( (p > 0.16, \text{CL}: 500 \text{ ms}) \), 4.8% \( (p > 0.08, \text{CL}: 1000 \text{ ms}) \), 5.1% \( (p > 0.05, \text{CL}: 2000 \text{ ms}) \), and 7.3% \( (p = 0.007, \text{CL}: 4000 \text{ ms}) \). Similar to before ischemia (C1 and I1) or without ischemia (C2), the longest mid-myocardial mean-APDs

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**Fig. 3. Spontaneous EADs and reentry in an ischemia-treated wedge.** The mean epicardial, midmyocardial, and endocardial APDs before ischemia (I1), after ischemia (I2), and after ATX-II (I3) are displayed at upper right. The APD contour maps (left, I1 and I3) show the transmural distributions of APD (in ms). The dot in the I3 map indicates the origin of EADs. EADs conducted around the mid-myocardial region having the longest APDs, reentered the region of origin, and terminated in the mid-myocardium (the arrow line). Selected traces of action potentials (I3, A–D) and the transmural ECG are displayed at the lower right. APDs in the I3 map were measured from the third APs. The wedge was paced at 1-s intervals.
were only slightly longer (≤2.5 ms, p>0.10) than the endocardial mean-APDs after the ischemia and reperfusion (I2, Fig. 2A–B). Therefore, APD and conduction velocity recovered well, and there was no excessive APD prolongation during slow rates, after >60 min of reperfusion in the eight wedges that completed the ischemia protocol.

Perfusion with 20 nmol/l ATX-II for >20 min significantly (p < 0.0001) prolonged the APDs and increased the transmural dispersion of APD in both groups at all pacing CLs with significantly more (p < 0.0001) effects in the ischemia group than in the control group (C3 and I3, Fig. 2A–B). ATX-II lengthened the APD significantly more (p < 0.05) in the mid-myocardium than in the epicardium and endocardium, at all pacing CLs in both groups (C3 and I3, Fig. 2A–B). The longest APDs occurred at deeper positions from the endocardium after (C3 and I3) than before ATX-II perfusion (C1, I1, C2, and I2, Fig. 2E). EADs and polymorphic VTs occurred in eight of eight (100%) and in seven of eight (87.5%) ischemia wedges, respectively, after ATX-II (I3, Fig. 2D). In contrast, there were no EADs or VTs in any of the eight control wedges without ischemia (C3, Fig. 2D). EADs originated in two sites simultaneously in one wedge. Subsequent activations in VTs were caused by both repetitive EADs and reentry. We observed epicardial, mid-myocardial, and endocardial origins of the repetitive EADs that caused the subsequent activations in VTs in one, seven, and four wedges, respectively. Episodes of transmural reentry that lasted for ≥1 loops were identified in two of the four wedges in which complete sequences of VT (from onset to termination) were recorded within the 5- or 10-s data segments. VTs were also identified in other three wedges in which only partial sequences of VT were captured within the data segments. EAD activations (from multiple foci) were responsible for 73%, and reentry for 18%, of the repetitive activations in the recorded VTs, and contributed to the sequen-

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**Fig. 4.** Spontaneous EADs and polymorphic VT in another ischemia-treated wedge. The mean epicardial, midmyocardial, and endocardial APDs before ischemia (I1), after ischemia (I2), and after ATX-II (I3) are displayed at upper left. The APD contour maps (I1 and I3s) show the transmural distributions of APD (in ms). Selected traces of AP (I3, from the sites A-D) and the transmural ECG are shown at the bottom. Activations (ACTs 1–9) and reentry are indicated below the traces. The APDs in the I3 contour maps are measured from ACT 4. ACTs 3 and 12 are lone EADs without triggering VT. ACTs 6–9 are rapidly oscillating focal EADs that triggered VT. The first I3 map shows the conduction of paced activations (ACTs 1, 2, 4, 5, 10, 11, and 13). The other I3 maps show the conductions of focal EADs and reentry (six loops).
tial alterations in the amplitudes and phases of the activation peaks in the transmural ECG.

Figs. 3 and 4 demonstrate examples of spontaneous EADs and the resulting reentry and VT after 40 min of ischemia, 60 min of reperfusion, and >20 min of ATX-II perfusion at 20 nmol/l (I3). Ischemia and reperfusion caused clear ($p < 0.05$), though small, increases of APDs (I2) from the baseline data (I1) in the wedge in Fig. 3. The longest APDs were at the endocardium both before and after the ischemia and reperfusion (I1 and I2). ATX-II lengthened APDs significantly (I3) with the longest APDs (>560 ms) in a mid-myocardial region (around site D in the I3 map, Fig. 3). Spontaneous EADs arose in another mid-myocardial region (around site A). Although an earlier EAD failed to conduct, a later EAD conducted around the long-APD region, blocked at D, which was refractory, and reentered the region of its origin (near A). Reentry terminated when the refractory core recovered its excitability. Spontaneous VTs occurred later in this wedge.

Fig. 4 shows the occurrences of EADs and VT in another wedge after ischemia, reperfusion, and ATX-II. The APDs in this wedge recovered well (without statistical differences) after >60 min of reperfusion (I2) to the baseline values (I1), from the effects of 40 min ischemia. There were neither EADs nor VTs before and after the ischemia and reperfusion (I1 and I2). ATX-II increased the APDs significantly, especially in the mid-myocardial region, and caused spontaneous EADs that resulted in VT (I3). The 10-s I3 data at the bottom of Fig. 4 contained seven paced activations (ACTs 1, 2, 4, 5, 10, 11, and 13), two lone EADs (ACTs 3 and 12), and a complete episode of VT (ACTs 6–9 and reentry). The two lone EADs (ACTs 3 and 12) arose from the endocardium without initiating VT. Another endocardially originating EAD (ACT 6) triggered VT, which consisted of repetitive focal activations (ACTs 6–9), arising in the sub-endocardium and mid-myocardium, and reentry. The lone EADs (ACTs 3 and 12) and the EAD that initiated the VT sequence (ACT 6) originated from the same endocardial region and initially conducted along similar paths (e.g., ACT 6). ACTs 6–8 propagated along two paths, a mid-myocardial–epicardial path and an endocardial path. ACTs 6–9 were blocked in the long-APD region near site C (Trace C, bottom of Fig. 4). Reentry occurred after the recovery of excitability in the region (after ACT 9 in Trace C). VT terminated after the last activation activated the entire area, terminating reentry.

4. Discussion

4.1. Major observations

This study showed that a transient episode of prior ischemia significantly enhanced the arrhythmogenicity and sensitivity of myocardium to ATX-II. The effects of 40 min of ischemia persisted after 60 min of reperfusion, despite recovery of APD and velocity of conduction from the effects of ischemia, and increased the responsiveness of myocardium to ATX-II. Although there were no VTs and no EADs in the wedges with ATX-II alone and VTs occurred in only 20% of the 10-wedge data. In contrast to the polymorphic VTs initiated by premature epicardial stimulation in isolated ventricular wedges [27], the polymorphic VTs in this study were initiated by spontaneous EADs following 40 min of ischemia, 60 min reperfusion, and ATX-II perfusion.

4.2. Potential mechanism

We observed good recovery of APD and velocity of conduction after 60 min of reperfusion from the effects of 40 min of no flow ischemia. Although >15 min of ischemia could uncouple intercellular gap junctions, similar reperfusion recovery was reported previously. It was demonstrated that rabbit papillary muscle recovered well, with nearly full restoration of gap junctional connections, conduction velocity, tissue resistivity, and resting membrane potential, after 30 min of reperfusion following 26 ± 1 min of no-flow ischemia (10 min after the onset of ischemia uncoupling) [28]. The initial episode of 5 min of ischemia preconditioning and O2 diffusion from the surrounding air to the mapping surface during ischemia could reduce the effects of the 40 min ischemia, thus facilitating the reperfusion recovery in this study.

Healthy ventricular myocytes have sufficient reserve in their ability to depolarize and then repolarize their membranes to generate action potentials and maintain cardiac function during physiological fluctuations of blood ionic concentrations, neuro-hormonal stimulation, and other minor perturbations. However, diseased or metabolically challenged myocytes (e.g., post-ischemia, post-infarction, post-tachycardia, heart failure, etc.) may have persistent remodeling that reduces the repolarization reserve [29]. Although this reduction may only have minor effects on normal electrical activity, it can cause excessive prolongation of APD, resulting in EADs...
and VT when there are additional inward currents (by ATX-II) or moderate potassium current inhibition [30].

Persistent myocardial remodeling was reported previously following infarction and tachycardia. Infarction remodeled rat right ventricular cells, reduced K+ channel expression, reduced K+ currents, prolonged APD, and elevated Ca2+ influx and [Ca2+]i, transients [31]. Short-term (0.5–2 h) rapid pacing altered the mRNA level of K+ channels in rat atrium [32]. One hour of rapid pacing superimposed on bradycardia prolonged ventricular APD and facilitated TdP induction for >3 h in canine hearts [33,34], imposed on bradycardia prolonged ventricular APD and or moderate potassium current inhibition [30].

When there are additional inward currents (by ATX-II) elicited rat right ventricular cells, reduced K+ channel following infarction and tachycardia. Infarction remodeled rat right ventricular cells, reduced K+ channel expression, reduced K+ currents, prolonged APD, and elevated Ca2+ influx and [Ca2+]i, transients [31]. Short-term (0.5–2 h) rapid pacing altered the mRNA level of K+ channels in rat atrium [32]. One hour of rapid pacing superimposed on bradycardia prolonged ventricular APD and facilitated TdP induction for >3 h in canine hearts [33,34], imposed on bradycardia prolonged ventricular APD and or moderate potassium current inhibition [30].

We postulate the following mechanism for our observations. Acute ischemia decreased the density of K+ currents [31], and reduced the repolarization reserve. The effects persisted after 60 min of reperfusion. Since healthy ventricular myocytes have sufficient repolarization reserve, partial reduction in repolarization reserve did not cause significant prolongation of APD. Thus, APD recovered well after 60 min of reperfusion. However, in this setting, the delayed inactivation of Na+ channels by ATX-II provided additional inward current to overwhelm the remaining repolarization reserve, causing an exaggerated repolarization delay. The repolarization delay triggered EADs, which produced multiple activations that conducted circuitously following the spatial distributions of repolarization heterogeneity. Both the focal EADs and reentry contributed to the repeated activations, resulting in polymorphic VT.

4.3. Effects of ATX-II in ventricular wedges

Most previous studies reported low arrhythmogenicity generated by 20 nmol/l ATX-II alone in ventricular muscle. ATX-II prolonged APD, but did not induce any EADs in canine ventricular tissue, although it induced EADs in Purkinje fibers [18]. EADs were observed in only 28% of the ATX-II-treated isolated rabbit ventricular cells [20]. In ATX-II-treated canine ventricular wedges, arrhythmias were not spontaneous, but could be initiated in 3 out of 12 wedges by abrupt acceleration of pacing CL to 250 ms, in association with T wave alternans [17]. However, the same group reported 50% occurrence of spontaneous VT in similar preparations [16,21]. We observed that the arrhythmogenicity of ATX-II (20 nmol/l) was low by itself, but increased markedly when combined with an episode of ischemia.

ATX-II increased the duration and wavelength of the action potentials. The prolonged activation wavelength could reduce the occurrence of reentry of the Na+ current-based excitation, especially in the small wedges. However, the VT in the current study was initiated by EADs that were likely based on Ca2+ current, due to their takeoff potentials at the plateau phase. Ca2+ current activates at reduced membrane potential than Na+ current, and thus, could oscillate rapidly during the plateau phase. The ATX-II–increased dispersion of repolarization contributed to the unidirectional block of conduction, which, combined with the rapid Ca2+ oscillations, could generate the observed short-wavelength VT. Although the isolated wedges could only accommodate VT with short wavelengths, intact hearts (e.g., as used by el-Sherif et al. [16]) could accommodate much longer reentry loops, and thus, could also support reentry based on Na+ activations.

4.4. M cells

We observed greater increases in the APD of cells located in the mid-myocardium during longer pacing CLs after ATX-II in both control and ischemia groups, but not before ATX-II (Fig. 2). The results of this study support the previous reports [16,17,21] of preferential mid-myocardial APD prolongation by ATX-II, as well as support the notion of minimal M cell effects in healthy isolated ventricular muscle [9–11] and in intact ventricles [12–14].

4.5. Experimental limitations

Cytochalasin D immobilizes muscle contraction by disrupting the F-actin filaments that form cytoskeleton. Although cytochalasin D has no identifiable effects on canine ventricular action potential (up to 80 μmol/l with microelectrode recordings [15]), it may prevent the opening of the stretch-activated channels secondary to immobilization and affect the channels that normally anchor to the cytoskeleton. These effects are unlikely to be significant, since this study used only 20–30 μmol/l, lower than the concentration of 80 μmol/l shown not to have any electrophysiological effects [15]. Although cytochalasin D does not affect canine ventricular AP, it affects AP in mouse heart [39], due to significant differences in the repolarization currents.

Since the isolated wedges are much simpler and smaller than intact hearts, the arrhythmias in wedges are only simple component mechanisms of clinical arrhythmias. Although we only mapped APs on the exposed transmural surface, intramural reentry, spiral, or scroll waves are unlikely to occur in the wedges, since the wavelength of intramural reentrant activity would exceed the thickness (4–7 mm) of the wedges.
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