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**Supporting Material**

# Mechanisms Underlying the Antifibrillatory Action of Hyperkalemia in Guinea Pig Hearts

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**Online Data Supplement**

## Methods

### Experiments

Animals were used according to institutional (SUNY Upstate Medical University Committee on Humane Use of Animals) and NIH guidelines.

### Data Analysis

*Dominant frequency (DF) of excitation:* DF maps were constructed by applying the fast Fourier transform to the fluorescent signals as previously described (1). A domain was defined as a continuous area on the DF map sharing a uniform DF value; domains were discarded from analysis if smaller than 1% of the mapped area. The domains of each DF map were classified in 0.5 Hz bins for construction of histograms by stacking the pixel number contained in each domain. To quantify the DF gradients between LV and RV, we subtracted the average DF values of 5x5 pixel areas located in the center of each chamber. DFmax was defined as the domain with the highest dominant frequency (1).

DF maps were classified as follows: a) maps corresponding to VF (i.e. multiple and complex waves); b) maps corresponding to VT (i.e., single or double activating waves). DF maps generated from VT movies occasionally exhibited pixels in the rotor tip vicinity with DF values double the rotation frequency, which were excluded from analysis.

*Time-Space Plot (TSP):* A frame-stack display is used to construct a TSP, as described elsewhere (2). Briefly, as shown in Figure 1C of the main article, the frame-stack display used here results from the compression of all data points of a given video frame along line xy-x'y' on the ventricular surface into a single line (represented at the bottom of each frame), and stacking all subsequent lines thus obtained (t1, t2, ..) onto one another to form a TSP. T is time; and S is horizontal distance. Planar waves are observed as diagonal excitation bands running from the site of initial activation. The slope of the activation band is inversely related to the conduction velocity (CV). Distance (time) between two consecutive excitation bands is the cycle length. During stationary rotor activity, excitation bands run from the center of rotation to the periphery. At the center, excitation bands are interconnected by bands of lower amplitude, which represent the activity around the core. Excitation bands are shifted in time at either side of the core. In the case of a drifting rotor, the center of interconnecting bands moves progressively with time in the direction of the drift.

*Phase Maps:* Phase movies were generated by applying the Hilbert transform to the fluorescent signals (3). Singularity points (SPs) were defined as points where all phases converged (4), and were identified automatically in all VF movies. The site of initiation of SPs was classified according to its location in the LV, in the RV, or in the LV-RV junction region (interventricular septum), which was defined as the area spanning 4-pixels on either side of the vessel running above the left anterior descending (LAD) coronary artery. In addition, in two movies of VF (one recorded in control and in an ensuing movie from the same heart recorded during perfusion with 10 mM $[K^+]_o$ just prior to conversion to VT) the SPs were classified into the following three categories according to the mechanism leading to termination (see Table 3): termination by 1)

block at a narrow isthmus separating two SPs; 2) fusion; 3) collision with an anatomical boundary. SPs drifting out of the field of view were discarded from this analysis.

Finally, to investigate the changes induced by hyperkalemia in the organization of VF we identified all sustained rotors (SPs fulfilling at least 4 complete rotations) at 4 mM $[K^+]_o$ (12 hearts) and 10 mM $[K^+]_o$ (7 hearts). For each individual rotation, we determined the ensemble of coordinate points $(x_R,y_R)$ defining the trajectory followed by the SP during the reentrant cycle. The rotation period (RP) was defined as: $(t_F-t_I)$, where $t_I$ and $t_F$ were respectively the times at initiation and termination of a single reentrant cycle. Provided that the SP trajectory was not always closed and convex during completion of a reentrant cycle (Figure 1S A), we estimated the rotor core area by calculating the area contained in the convex hull (5) of the trajectory of each rotation (Figure 1S B**)**. Specifically, from the ensemble of points $(x_R,y_R)$ we used Graham's Scan algorithm (5) to calculate the unique subgroup of points $(x_{Rc},y_{Rc})$ that defined the smallest convex polygon for which each of the points in the original ensemble $(x_R,y_R)$ was either in the boundary or the interior of $(x_{Rc},y_{Rc})$. The area inscribed in the wave-tip trajectory during a single complete rotation was determined by calculating the area contained in the polygon defined by the convex-hull points $(x_{Rc},y_{Rc})$, and used as a surrogate of the core area. The aforementioned parameters for each sustained rotor were expressed as an average over the total number of rotations fulfilled by the rotor. Thus, as summarized in Figure 3 of the main manuscript, for each sustained rotor we quantified the mean core area (MCA) and the mean of the rotation period (MRP).

**Computer Simulations**

We utilized the Luo & Rudy dynamic model (6) of the guinea pig ventricular myocyte to simulate spiral wave reentry in a two-dimensional (2D) ventricular sheet. To improve similarity with experimental results we incorporated the following changes into the single-cell formulation: 1) The maximum conductance of the sodium current was reduced to 12.8 following a recent canine ventricular myocyte model by Fox *et al.* (7). This gives a maximum upstroke velocity of approximately 300 V $s^{-1}$ at 5 Hz pacing of the single cell. 2) The formulation of $I_{K1}$ was replaced by the corresponding equation in that same model (7), which provided an $I_{K1}$ rectification more similar to experimental values (8) at the corresponding $[K^+]_o$ concentration (Figure 2S). 3) The maximum conductance value of the $I_{Ks}$ current was increased such that the ratio of $I_{Ks}/I_{Kr}$ conductance was 23.0, which better represented an epicardial cell (9). 4) The time constants of the voltage dependent activation and inactivation of the L-type $Ca^{2+}$ current ($I_{CaL}$) were replaced by recent formulations based on experimental data obtained in guinea pig ventricular myocytes at physiological temperatures (10). 5) The density of $I_{CaL}$ was reduced by 30%, and the formulation of the $Ca^{2+}$-dependent inactivation of $I_{CaL}$ was made similar to that found in the Fox *et al.* model (7). The revised cell model was then incorporated into a 2D sheet (4×4 cm), and rotors simulated by cross-field stimulation similar to a recent theoretical study (11). LV/RV heterogeneity was implemented as follows: the maximum ionic conductances of RV $I_{K1}$, $I_{Kr}$ and $I_{Ks}$ were 60%, 75%, and 75% of their respective values in the LV. Similarly, $Ca^{2+}$-dependent inactivation of $I_{CaL}$ was stronger in LV.

As illustrated in Figures 6 and 7 of the main article, incorporation of the above modifications into the Luo & Rudy model enabled simulation of an LV high frequency stable rotor (≈30 Hz), with fibrillatory conduction towards the RV (≈18 Hz), which closely resembled our control

experiments. Upon initiation of a rotor in the presence of 4.0 mM $[K^+]_o$ for a duration of 2 seconds, we studied the effect of hyperkalemia on reentry frequency and dynamics by gradually increasing values of $[K^+]_o$ to 5.0, 6.0, 7.0, 8.0 and 9.0 mM for a duration of 1 second each (Reentry termination at 9.0 mM $[K^+]_o$ precluded 10.0 mM $[K^+]_o$ analysis). The duration of the reentry simulation was constrained by the large run time (≈ 5 days) on a parallel 32 processor cluster, and by the inability to sustain stable reentry for more than 1 second at $[K^+]_o$ concentrations >6.0 mM.

Given that both the maximum conductance and the reversal potentials of $I_{K1}$ and $I_{Kr}$ currents are dependent on $[K^+]_o$, we performed an additional set of simulations (see Figure 7 in main article) in which we independently clamped the maximum conductance and/or the reversal potentials to control values (i.e. their respective values at 4 mM $[K^+]_o$), during a simulated increase of $[K^+]_o$. This simulation was repeated for $I_{K1}$ and/or $I_{Kr}$.

We conducted additional simulations, where after initiation of a rotor in the presence of 4.0 mM $[K^+]_o$ for a duration of 2 seconds, we blocked the conductance of $I_{K1}$ at increasing values (from 10% to 90% blockade, in steps of 10%), to see if our model could account for the previously reported experimental effects of $BaCl_2$ on VF (see Figure 7S).

We measured CV measured as a function of the distance from the core, as described previously (12). As illustrated in Figure 3S, and as expected for both experiments and simulations at 4mM (12), CV is slowest near the core and increases progressively as a function of distance from the core.

*Statistical analysis:* One-way ANOVA was used to analyze mean DF (DFmean), DFmax, number of DF domains per unit area, and largest DF domain during control, hyperkalemic VF and VT, and washout conditions, as well as for comparison of the MCA, and MRP during control, and hyperkalemic VF and VT. Two-tailed $\alpha$ was set to 0.05. Tuckey's test was used for pair-wise comparison of means in each group. Paired Student's t-test was used to compare SP density during control and hyperkalemia.

## Online Results

### *Effect of 10 mM $[K^+]_o$ on wavelet organization*

We considered that a rotor was sustained when it underwent >4 cycles. Figure 4S, A-C (Movies 1-3) compares the wave propagation dynamics associated with single reentrant cycles in control (4S A), 10 mM $[K^+]_o$ VF (4S B) and VT (4S C). Each panel shows three snapshots corresponding to a full rotation of the main rotor under each condition. The cycle lengths were 23 ms, 57 ms and 67 ms in A, B and C, respectively. It is clear that, the longer the cycle length the lesser the number of peripheral SPs. Expectedly, the DFmax of the three aforementioned movies (36.5, 21.5, and 16 Hz respectively) correlated well with the increasing cycle lengths of the rotors (not shown).

### *Transitions between VF and VT*

Figure 5S A demonstrates how during VF in hyperkalemia (10 mM), annihilation of a previously sustained rotor at the LV-RV junction region resulted in a transition to VT of slower frequency

(Movie 4). During the first three rotations (maps labeled 1-3), waves emanating from the rotor (rotation period: 56-57 ms) propagated to the RV. However, during the fourth rotation (from 172 to 183 ms), propagation failed at the LV-RV boundary and two counter-rotating daughter wavelets were created. At 195 ms, one of the two daughter wavelets invaded the sustained rotor core region, and blocked further excitation progress (Figure 5S A). Instants later, the second daughter wavelet was annihilated by interaction with a third wavelet incoming from the lower LV, which thus eliminated all SPs from the mapped region (movie 4). After a 78 ms pause between maps labeled 195 ms and 273 ms in Figure 5S A, and between optical action potentials labeled 4 and 5 in Figure 5S B, ventricular activation was taken over by a single wave (activation in map 5) originating outside of the field of view somewhere in the LV (Figure 5S A), followed by other single wave activations (cycle length>72 ms) from varying locations which finally stabilized close to the apex and outside of the mapped region (maps 6 and 7 and movie 4). Upon restoring 4 mM $[K^+]$o the VT frequency accelerated and finally converted to VF with a similar DF distribution as in control (not shown). Importantly, in four hearts exhibiting VF to VT transitions in hyperkalemia, the VT frequency was always lower than the DFmax of all VF episodes recorded in the same heart. Figure 5S C shows the statistical comparison between the DFmax of the preceding VF episode and the ensuing VT (19.6±4.5 to 14.3±2.3 Hz, p=0.024).

***Spatial distribution of voltage and excitability in simulations***

To further determine the mechanism leading to slowing of excitation during hyperkalemia, we plotted snapshots of voltage (Figure 6S, left) and of the underlying inactivation of the gating variables ('hj') of the sodium current $I_{Na}$ (Figure 6S, right) during simulated reentry in control, and 7.0 and 9.0 mM $[K^+]_o$. The voltage maps show that by increasing potassium concentration the wavelength becomes progressively shorter and the diastolic potential more depolarized (-92.2 vs -80.2 vs -73.0 mV during control, 7 mM, and 9 mM $[K^+]_o$, respectively). This results in a progressively reduced recovery of sodium current availability (maximum value of 'hj' is 0.888 vs 0.969 vs 0.524 during control, 7 mM, and 9 mM $[K^+]_o$, respectively). Thus, a reduction of the excitability of the tissue within the excitable gap during reentry (note the transition from significant regions depicting dark orange right ahead of the reentering wavefront in control, to a very reduced pale yellow region in front of the wavefront during 9 mM $[K^+]_o$) underlies the reduction of the conduction of the wavefront, which ultimately leads to drift and termination of reentrant waves during hyperkalemia.

***Effect of blocking $I_{K1}$ on the simulated rotor***

One question that arises from our results is whether the antiarrhythmic effect of extracellular $K^+$ on rotor dynamics is similar or different to the observed antiarrhythmic effects of $I_{K1}$ blockade, as seen in the presence of barium in experiments (3). To answer this question via simulations, $I_{K1}$ was increasingly blocked (from 10% to 90%, with 10% steps), and the results are shown in Figure 7S. Panel A shows representative action potentials from a single point in the LV. It can be seen that there is a progressive depolarization of the resting membrane potential, as would be expected with $I_{K1}$ block (13), and is similarly seen during hyperkalemia (Figure 8A in main manuscript). However, the APD is now increased, in contrast to hyperkalemia, where APD was decreased. The frequency of excitation of the rotor during $I_{K1}$ blockade is compared by plotting DF maps in panel B of Figure 7S, where the DF maps are shown in control (left), when $I_{K1}$ is blocked 50% (center), and when $I_{K1}$ is blocked 90% (right). As with hyperkalemia, the DFmax decreases with increasing block of $I_{K1}$. In panel C, the DF at point "x" in panel B is plotted for

different values of $I_{K1}$ blockade, and is seen to decrease non-linearly. The simulated rotor is terminated when $I_{K1}$ blockade is 90%, and the DF before termination is ≈ 10 Hz, which is similar to the behavior seen in experiments (3). Thus these results show that although the APD is increased when $I_{K1}$ is blocked, the depolarization of the resting membrane potential reduces excitability, decreasing the dominant frequency, and eventually terminating the rotor. This is the common mechanism underlying the antiarrhythmic effect of both $I_{K1}$ blockade and hyperkalemia.

**Clinical Implications**

In the clinical setting, VF usually elicits global ischemia which may in turn alter VF dynamics (15-17). A recent study showed that hyperkalemia was the single most important factor responsible for determining excitation changes during ischemia in the fibrillating rabbit heart (18). Thus our study provides insights into the mechanisms that might determine VF evolution and its organization on account of accumulation of $[K^+]_o$, and perhaps its subsequent efficient cardioversion in patients (19). Lastly, most subjects do not undergo an arrhythmic episode during exercise despite and increased sympathetic output. This is partially attributed to a simultaneous increase of $[K^+]_o$ during exercise. Thus our study is also relevant in underlining the protective effects of hyperkalemia during exercise against sustained arrhythmias (20).

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## TABLES

| | Control VF (n=5) | 7 mM $[K^+]_o$ VF | Control VF (n=7) | 10 mM $[K^+]_o$ VF | 10 mM $[K^+]_o$ VT |
|---|---|---|---|---|---|
| DFmax (Hz) | 31.5±4.7 | 23.0±2.3* | 31.2±4.7 | 19.5±3.6* | 14.0±1.8* |
| DFmean (Hz) | 15.0±3.0 | 15.9±2.1 | 13.4±2.6 | 13.3±2.4 | 13.4±2.1 |
| LV-RVDF (Hz) | 14.7±5.0 | 4.4±1.3* | 14.8±2.7 | 3.2±1.4* | 0.0±0.0* |
| Largest Domain DF (Hz) | 12.5±1.4 | 16.8±1.0* | 13.5±2.5 | 14.6±5.1 | 13.9±1.9 |
| Domains/Area ($1/mm^2$) | 8.7±2.3 | 6.2±1.0 | 8.6±1.8 | 5.8±2.0¶ | 1.0±0.5*† |

(*p<0.006 vs control VF. ¶p<0.05 vs control VF. †p<0.001 VT vs 10 Mm $[K^+]_o$ VF).
**Table 1.** DF parameters calculated during control VF and hyperkalemic VF or VT episodes.

| | Control (6/12 hearts) | | 10 mM $[K^+]_o$ (5/7 hearts) | | | |
|---|---|---|---|---|---|---|
| | VF | | VF | | VT | |
| | LV | RV | LV | RV | LV | RV |
| # Rotors | 18 | 1 | 15 | 5 | 36 | 5 |
| MCA ($mm^2$) | 0.90±0.53 | 4.78 | 2.11±0.91* | 4.90±3.86¶ | 1.97±0.89* | 7.14±2.78 |
| MRP (ms) | 27.6±3.0 | 60.4 | 56.1±8.3* | 56.5±10.0 | 66.7±8.2*† | 73.1±0.5 |

(*p<0.001 vs control VF (LV). †p<0.001 VT vs 10 Mm $[K^+]_o$ VF (LV); ¶p<0.05 RV compared to LV).
**Table 2.** Parameters of sustained rotors SPs identified during control VF and 10 mM VF or VT episodes.

| **Termination** | **#SP** | **BK (%)** | **FS (%)** | **CB (%)** |
|---|---|---|---|---|
| **Control (0.5 s)** | 120 | 84.1 | 14.2 | 1.7 |
| **10 mM $[K^+]_o$ (1 s)** | 103 | 85.4 | 8.7 | 5.8 |

BK, Block; FS, fusion; CF, conduction failure; CB, collision boundary;
**Table 3.** Percentage contribution of mechanisms leading to termination of SP.

## Supplement Videos

**Movie 1.** Movie of phase of excitation recorded from the anterior (top) and anterior (bottom) ventricular walls during control VF. White pixel indicates location of sustained rotor SP. Playback speed reduced (X80).

**Movie 2.** Movie of phase of excitation recorded from the anterior (top) and anterior (bottom) ventricular walls during VF and perfusion with 10 mM $[K^+]_o$ solution. White pixel indicates location of sustained rotor SP. Playback speed reduced (X80).

**Movie 3.** Movie of phase of excitation recorded from the anterior (top) and anterior (bottom) ventricular walls during VT and perfusion with 10 mM $[K^+]_o$ solution. White pixel indicates location of sustained rotor SP. Playback speed reduced (X80).

**Movie 4.** Movie of phase of excitation recorded from the anterior ventricular wall during a transition from VF to VT occurring during perfusion with 10 mM $[K^+]_o$ solution. White pixel indicates location of sustained rotor SP. Playback speed reduced (X80).

**Movie 5.** Excitation waves of a simulated episode of VF during control and gradually increasing steps of $[K^+]_o$.

**Movie 6.** Movie of a simulated rotor when $I_{K1}$ is blocked from 10% to 90%, in steps of 10%.

## Supplement Figure Legends

**Figure 1S A.** Trajectories followed by the rotor tip during completion of a cycle of three SPs identified in control (left), 10 mM$[K^+]_o$ VF (center), and 10 mM$[K^+]_o$ VT (right). **B.** Area (light grey) enclosed by the convex hull of the trajectories depicted in panel A.

**Figure 2S.** Simulated current-Voltage (I-V) relationship of $I_{K1}$ at different concentrations of $[K^+]_o$.

**Figure 3S.** Local conduction velocity as a function of the distance from the core for an experimental rotor (A) and for a simulated rotor (B) in control (4 mM$[K^+]_o$) conditions. Left panels: Activation maps determined during one rotation of rotors. Right panels: Corresponding plots of mean (±S.D.) local CV versus distance to the core.

**Figure 4S**. Sustained rotors and SP during VF. **A-C**: Snapshots of excitation phase on anterior wall, depicting a complete cycle of three sustained rotors (black and white circles) identified during control (**A**), 10 mM$K^+$ VF (**B**), and during a 10 mM$K^+$ VT episode (**C**). Black circles indicate the location of peripheral SP. Arrows indicate direction of rotation.

**Figure 5S.** Termination of VF. **A.** Phase snapshots depicting VF to VT transition during 10 mM $[K^+]_o$ perfusion. Labels 1-7 on upper left corner of phase snapshots indicate correspondence to optical action potentials numbered 1-7 (black arrows in panel **B**) of fluorescent signal recorded from single pixel (white asterisk). White arrows indicate direction of excitation propagation. **C.** Mean DFmax of VT and preceding 10 mM $[K^+]_o$ VF episodes (n=4). *p=0.024, VT vs VF.

**Figure 6S**. Excitability during reentry. Spatial distribution of transmembrane voltage (left) and inactivation gating variables ('hj' gates, right) of the $I_{Na}$ during stable reentry in control (A), 7 mM $[K^+]_o$ (B), and 9 mM $[K^+]_o$ (C) conditions.

**Figure 7S**. Effect of blocking $I_{K1}$ on rotor. **A.** Shows representative action potentials from a single point in the left ventricle for 200 msec, in control (left), when $I_{K1}$ is blocked 50% (center), and when $I_{K1}$ is blocked 90% (right). **B.** Dominant frequency map of the 2D simulated rotor, in control conditions (left), when $I_{K1}$ is blocked 50% (center), and when $I_{K1}$ is blocked 90% (right). **C.** Dominant frequency of a single point in LV (marked by "x" in panel B) as IK1 is blocked from 10% to 90%.