# Transmural $I_{K(ATP)}$ Heterogeneity as a Determinant of Activation Rate Gradient During Early Ventricular Fibrillation: Mechanistic Insights from Rabbit Ventricular Models

## ONLINE SUPPLEMENT

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**Glossary**

**APD:** action potential duration, **AR:** activation rate, **$I_{K(ATP)}$:** ATP-sensitive potassium current, **PS:** Purkinje system, **PMJ:** Purkinje-myocardial junction

## *A. Experimental Approach for Recording Electrograms (Fig. 1A)*

Fig. 1A shows illustrative examples of differential rate using selected unipolar electrograms from both endocardial and epicardial arrays deployed in an isolated pig heart and a human cardiomyopathic heart, both in Langendorff perfusion preparations. The human electrograms shown in the figure were recorded in VF during a simulated VF arrest protocol at 3 minutes of ischemia, while the pig data was recorded during a perfused VF protocol also at 3 minutes. Electrograms were recorded from endocardial and epicardial electrode arrays, each having 112 electrodes. The electrograms were amplified, filtered [0.5 – 200 Hz] and digitized at 1000 samples per second using a custom-made data acquisition system[1, 2]. All swine experiments were approved by the Animal Care Committee of the University Health Network and conformed to the guidelines in the "Guide to the Care and Use of Laboratory Animals" published by the National Academy Press. Human data were obtained during a previous study[2] from explanted hearts from patients with cardiomyopathy who underwent transplantation; however, the particular electrograms shown here have never been published. The research protocol and patient consent forms were approved by the University Health Network Ethics Board and the investigation followed the principles outlined in the Declaration of Helsinski.

## *B. Calculation of Moran's I in Bullseye Plots for Endocardial/Epicardial AR*

Moran's I is a measure of spatial autocorrelation[3] given by:

$$I = \frac{N}{\sum_i \sum_j w_{ij}} \frac{\sum_{i=1}^{N} \sum_{j=1}^{N} w_{ij}(X_i - \mu_X)(X_j - \mu_X)}{\sum_{i=1}^{N} (X_i - \mu_X)^2} \quad (1)$$

where $X_k$ is the value measured at location $k$, $\mu_X$ is the mean of all $N$ values, and $w$ is an $N$-*by*-$N$ matrix of weight coefficients, such that $w_{ij}$ is 1 if locations $i$ and $j$ are neighbors and 0 otherwise. As indicated in the text, Moran's I values vary between −1, indicating perfect dispersion, and 1, indicating perfect uniformity. A random pattern results in a value of zero.

## *C. Ping-Pong in the PS During Early VF*

Previous in silico exploration of ping-pong in the PS required careful a priori modifications of the tissue in question[4] (i.e., "different sites in the His-[PS] had different heart rate thresholds for [delayed afterdepolarization]-induced bigeminy"). We observed numerous spontaneously-occuring intervals of this curious behavior during episodes of VF. One such example is shown in Movie 5.

## *D. Movie Captions*

**Movie 1:** Spatial $V_m$ maps (same scale as Fig. 4) for a 1000 ms sequence from just after S2 in a model with high $I_{K(ATP)}$ throughout the myocardium and no PS. Average epicardial and endocardial ARs are 13.4 and 13.1 Hz, respectively. See Fig. 4A.

**Movie 2:** Spatial $V_m$ maps (same scale as Fig. 4) for a 1000 ms sequence from just after S2 in a model with high-$I_{K(ATP)}$ epicardium, low-$I_{K(ATP)}$ endocardium, and no PS. Average epicardial and endocardial ARs are 12.1 and 9.11 Hz, respectively. See Fig. 4B.

**Movie 3:** Spatial $V_m$ maps and traces from 3 epicardial points (same scales as Fig. 6A&B) for a 2000 ms sequence in a model with medium-$I_{K(ATP)}$ epicardium, low-$I_{K(ATP)}$ endocardium, and sub-epicardial PS. ARs in the black, red, and blue traces are 13, 10.25, and 12.25 Hz, respectively. See Fig. 6A-C.

**Movie 4:** Spatial $V_m$ maps and traces from 3 endocardial points (same scales as Fig. 6D&E) for a 2000 ms sequence in a model with high-$I_{K(ATP)}$ endocardium, low-$I_{K(ATP)}$ epicardium, and sub-endocardial PS. ARs in the black, red, and blue traces are 10.75, 9.5, and 10.5 Hz, respectively. See Fig. 6D-F.

**Movie 5:** Simultaneous $V_m$ maps (same scale as in Fig. 4) of the PS (left), ventricular endocardium (center), and epicardium (right) for a 1-second interval during VF. In the model shown, PMJs are sub-endocardial and $I_{K(ATP)}$ channel expression is moderate throughout the ventricles ($f_{ATP}$ = 0.112%). Retrograde activation of the right and left arborizations of the PS alternates for the 5 several cycles – on both the left and right sides, excitation originates at a distal PMJ then excitation spreads rapidly before blocking in the refractory bundle branches. On the cycle #6, excitation from the right arborization traverses

the His bundle and partially activates the left side of the PS. On cycle #7, right fascicular activation is delayed and excitation from the left arborization propagates farther into the right bundle branch than on any previous cycle. Finally, on cycle #8, PS activation sequence is completely left to right.

## *D. References used in Online Supplement*


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