Spatial dispersion of repolarisation and vulnerability to re-entry in cardiac tissue: a model study

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1. Introduction

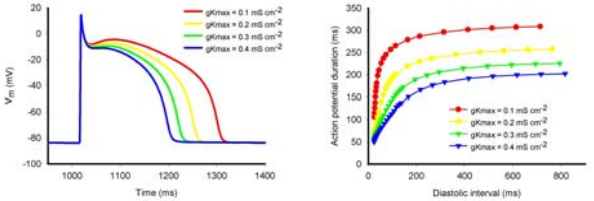
Spontaneous episodes of ventricular tachycardia (VT) and ventricular fibrillation (VF) are usually associated with hearts whose cell and tissue properties have been altered by disease or congenital abnormality. Abundant experimental evidence supports the idea that VT and VF are sustained by re-entry, but the initiation of re-entry is not well understood.

The purpose of this study was to investigate how measured APD dispersion and vulnerability to re-entry are related to: (i) the spatial scale of heterogeneity, (ii) the magnitude of differences in K^+ channel conductance between regions with short and long APD, and (iii) cell-to-cell coupling. In order to control these parameters independently, we used a computational model of ventricular tissue

2. Methods

We used a monodomain model of cardiac tissue [1], described by the Luo-Rudy version 1 (LR1) model of cardiac ventricular myocytes [2]. We varied APD by changing the maximum conductance of the K^+ channel *gKmax* (Fig. 1). Each virtual tissue was a 60 × 60 mm 2D sheet with a 10 mm border around each edge where *gKmax* was set to 0.004 mS mm^{-2} (short APD). The central 40 × 40 mm region was subdivided into alternate squares where *gKmax* was either 0.004 mS mm^{-2} (short APD) or a lower value (long APD).

Figure 1. AP shape and APD restitution curve for different values of *gKmax*



3. Results

The effect of changing spatial scale, ionic heterogeneity, and coupling on the spatial and temporal distribution of APD is shown in Fig. 2 and Fig. 3. Increased spatial scale of heterogeneity, increased magnitude of ionic heterogeneity, and decreased coupling all acted to maximise APD dispersion.

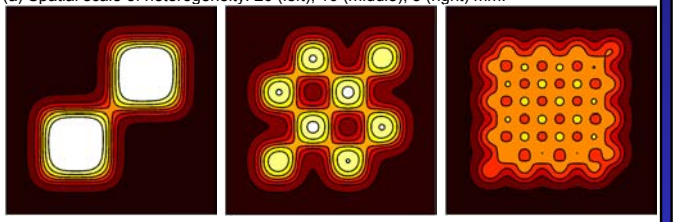
A premature S2 stimulus to the bottom edge resulted in either block, re-entry, wavebreak, or propagation as the S2 interval increased (Fig. 4 and Fig. 5). We defined the vulnerable window as the range of S2 intervals that elicited either wavebreak or re-entry, and we found good aggreement *(R^2 = 0.99)* between vulnerability and *APDdiff*, the simplest measure of APD dispersion (Fig. 6). The intercept of the regression line with the *APDdiff* axis suggested that for this model configuration, an APD dispersion of > 20ms was needed for re-entry to be initiated with a premature S2 stimulus.

4. Conclusion

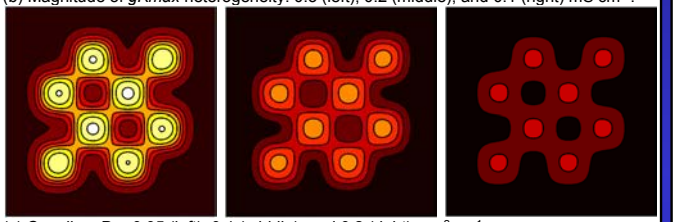
This study has shown that a simple measure of APD dispersion is a good predictor of vulnerability to re-entry. We have also highlighted the important effect of electrotonic current flow during repolarisation, which can act both to smooth regional differences in APD and to reduce the vulnerable window for re-entry.

Figure 2. Effect of changing spatial scale, ionic heterogeneity, and coupling on APD distribution. White indicates APD of >250 ms, black APD of <180ms. APD contours at 10ms intervals. Steady pacing from bottom edge with cycle length of 500 ms.

(a) Spatial scale of heterogeneity: 20 (left), 10 (middle), 5 (right) mm.



(b) Magnitude of *gKmax* heterogeneity: 0.3 (left), 0.2 (middle), and 0.1 (right) mS cm^{-2}.



(c) Coupling: D = 0.05 (left), 0.1 (middle), and 0.2 (right) mm^{2}ms^{-1}.

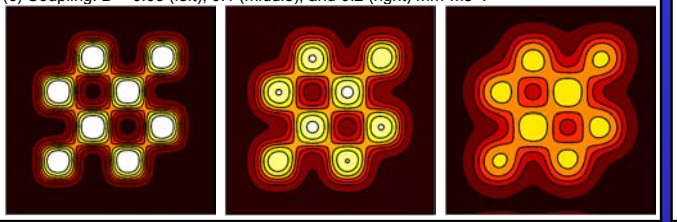


Figure 3. Effect of heterogeneity on maximum difference in APD (APDdiff), SD of differences in APD (APDSD), and maximum local difference in APD between sites 1mm apart (MaxLD)

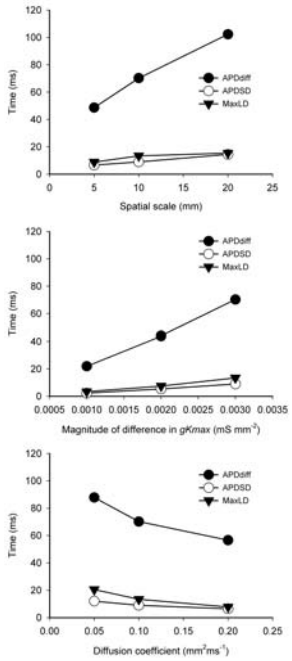


Figure 5. Response of models with varying spatial scale (left), ionic heterogeneity (middle), and coupling (right) to premature S2. Blue indicates block, orange re-entry, red wavebreak, and purple propagation without wavebreak.

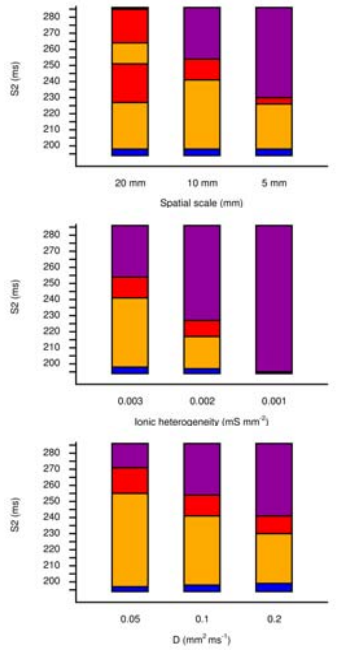


Figure 4. Example of re-entry (S2 230 ms, left), wavebreak (S2 250 ms, middle), and propagation (S2 265 ms, right) for model with spatial scale of 10 mm (blue squares), ionic heterogeneity of 0.3 mS cm^{-2}, and D of 0.1 mm^{2}ms^{-1}. Propagation from bottom to top, with brighter colours showing later activation. Isochrones are at 5 ms intervals, with activation front at S2+100 ms shown as thick line.

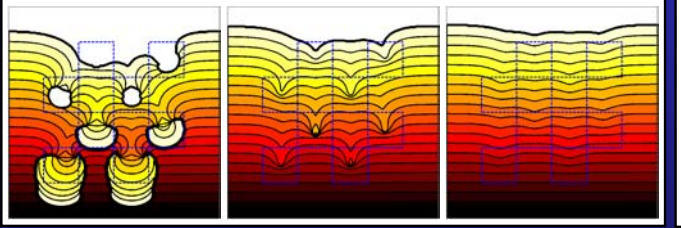
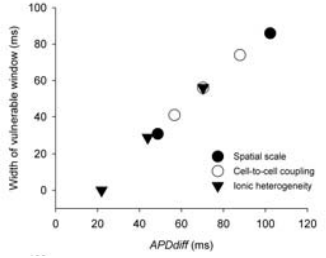


Figure 6. Width of vulnerable window plotted against *APDdiff*



4. References

[1] Clayton, R. H. (2001). *Physiological Measurement* **22**(3): R15-R34.

[2] Luo, C.-H. and Y. Rudy (1991) *Circulation* **68**: 1501-1526.

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This work is supported by the EPSRC (GRS43498/01), and the British Heart Foundation (PG/03/102/15852)