Effect of transmural variations in action potential duration on re-entry in a computational model of mammalian ventricular myocardium

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Introduction

Ventricular fibrillation (VF) is a deadly cardiac arrhythmia, and the likely mechanism is breakdown of a single re-entrant wave. Several mechanisms for breakdown have been proposed including steepness of the action potential duration (APD) restitution curve (Garfinkel *et al* PNAS 2000;97:5681-6238) and the effect of rotational anisotropy in the ventricular wall (Fenton and Karma Chaos 1998;8:20-47). The aim of this study was to investigate whether transmural variations in APD are another possible mechanism.

Transmural difference in APD

We varied APD by changing the parameter u^{si}_c in the FK excitability model. This parameter controls the time course of the slow input current, and reducing u^{si}_c from 0.85 to 0.50 prolongs the action potential without greatly affecting its shape. In 3D simulations a linear change in u^{si}_c from top to bottom produced a linear change in APD.

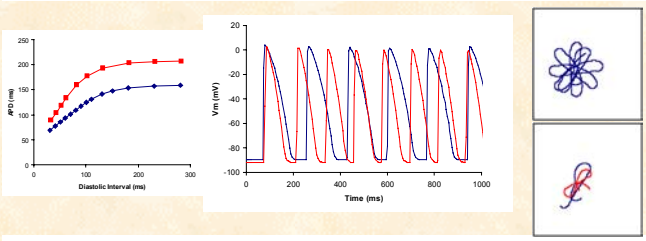


Figure shows APD restitution curves (left) for tissue with normal (red) and prolonged (blue) APD. Action potentials (middle) recorded during stable re-entry in homogenous isotropic slabs, showing periods of 115 ms for normal (red) and 160 ms for prolonged (blue) APD. Meander pattern for tissue with prolonged APD (right top). Meander patterns for 200 ms of re-entry showing faster rotation in tissue with normal APD (red).

Computational model

We simulated action potential propagation using the 3D cable equation, with excitability described by the Fenton Karma (FK) model and restitution set to reproduce that of the modified Beeler Reuter model [Chaos 1998;8:20-47]. The model was solved using explicit forward differences with a time step of 0.1 ms, a space step of 0.33 mm, and no-flux boundary conditions. We simulated re-entry in slabs of tissue 10 and 20 mm thick, with and without 120° rotational anisotropy between top and bottom surfaces.

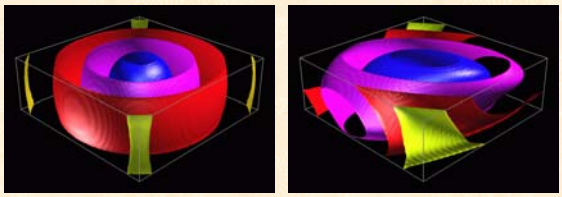
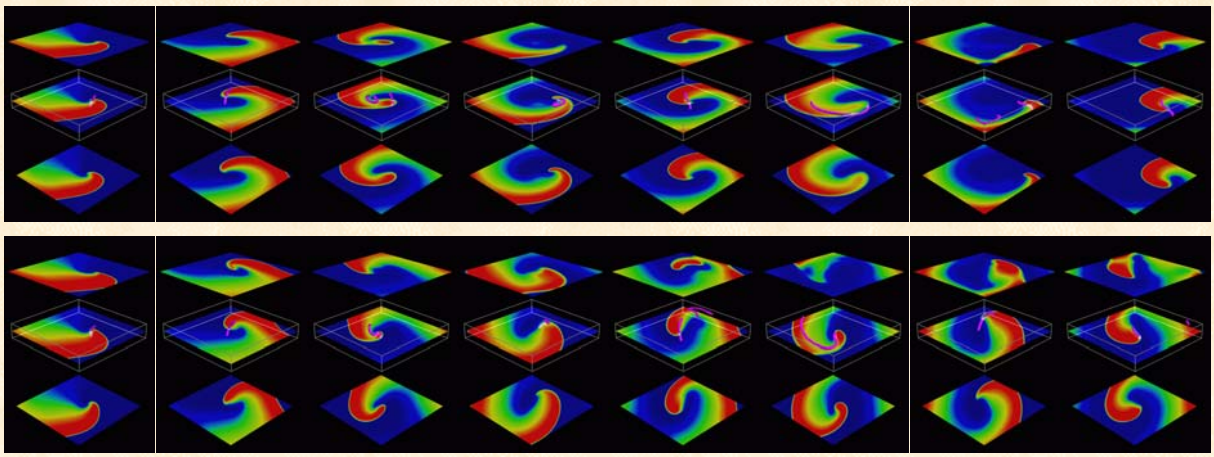


Figure shows action potential wavefronts in simulated 60 x 60 x 20 mm slabs resulting from a point stimulus at the centre. In an isotropic slab with D=0.1 mm^2ms^{-1} (left) surfaces show wavefronts 20 (blue), 40 (pink), 60 (red) and 80 ms (yellow) after stimulation. In an anisotropic slab with D along fibres = 0.2 mm^2ms^{-1} and D across fibres = 0.05 mm^2ms^{-1} (right) surfaces show wavefronts 40 (blue), 60 (pink), 80 (red) and 100 (yellow) after stimulation.

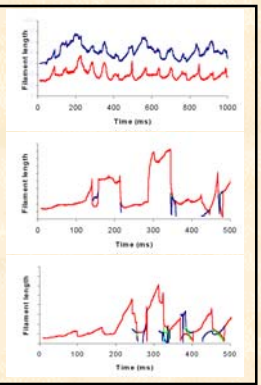
Results

In both 10mm and 20mm thick simulated slabs with a transmural difference in APD, the single initial re-entrant filament broke into secondary filaments. In the isotropic simulations, a single filament continued to dominate and the scondary filaments were short lived whereas in anisotropic simulations the number of secondary filaments was greater and they were longer lived.



Example snapshots showing breakdown of re-entry between 50 and 400 ms after initiation with a single untwisted wave in isotropic (top) and anisotropic (bottom) 6 x 6 x 1 cm tissue with a linear decrease in APD from top to bottom. Membrane voltage is colour coded from blue (resting) to red (active) and filaments are shown in pink.

The mechanism of breakdown with APD differences appears to be accumulated filament twist resulting from a difference in rotation period. Twist results in elongation and buckling of the filament, which then fragments when it touches a boundary. In simulated anisotropic simulations with no APD difference twist is accumulated and then lost as the re-entrant wave rotates, and this can be seen as fluctuations in filament length (right, top) for 1 cm (red) and 2 cm (blue) simulations. In both isotropic (right, middle) and anisotropic (right, bottom) tissue twist is not lost unless the filament touches a boundary. The interaction of a filament with a boundary lead to short lived daughter filaments in isotropic simulations, but in anisotropic simulations the daughter filaments were more persistent.



Conclusions

We have shown that transmural differences in APD can have a destabilising influence on re-entry with a transmural filament because there is a transmural gradient in the period of re-entry. This gradient results in accumulated twist in the filament, and breakdown of re-entry occurs when the twisted and elongated filament touches a boundary.

We conclude that in the simplified FK model with MBR restitution, modest transmural differences in APD result in accumulated filament twist and contribute to filament breakup. Further studies with different models of excitability and a range of parameter values are needed to establish if these findings are model dependent, although preliminary data using the LRD models for endocardial and epicardial cells show different rotation periods.

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