Cardiac structure and electrical activation: models and measurement

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Re-entrant arrhythmia and fibrillation are three-dimensional (3D) events that involve relatively large tissue volumes and are influenced by regional variation of the electrical properties of cardiac tissue and by the complex architecture of the heart. Within this context, computer models that incorporate realistic descriptions of cardiac anatomy and the electrical properties of myocardium provide a powerful tool with which to interpret and interpolate experimental observations.

Our group has systematically measured the 3D geometry of right and left ventricles in dog and pig hearts, and has characterised myocyte orientation throughout the ventricular wall in these species. These data have been incorporated into a detailed finite element model of cardiac anatomy which has been used by ourselves and others to study normal electrical activation and re-entrant arrhythmia.

We have developed a confocal imaging technique that enables us to reconstruct the 3D organisation of cardiac myocytes and extracellular collagen matrix in relatively large tissue volumes at up to 1μm voxel resolution. Morphometric studies employing this approach confirm that ventricular myocardium is a complex hierarchy in which myocytes are arranged in discrete layers separated by cleavage planes that are relatively extensive, particularly in the left ventricular (LV) midwall.

The effect of structural discontinuity on the propagation of electrical activation has been modelled using a finite element formulation in which the electrical properties of intracellular and extracellular domains are explicitly represented. Detailed information on 3D cleavage plane organisation and muscle fibre orientation, extracted from an extended volume image of a transmural segment of rat LV myocardium, was incorporated into the model. For an ectopic midwall stimulus, the predicted spread of electrical activation was initially non-uniform and markedly affected by the discontinuous 3D arrangement of muscle layers.

The model has been validated by recording extracellular potentials at up to 36 sites within the LV free wall in sinus rhythm and during intramural pacing. *In situ* measurements were made first in an anaesthetised (Zoletil, 10mg/kg im, initially and then 2-5% halothane in oxygen), ventilated open-chest pig preparation and comparable data were then recorded with the hearts isolated and mounted in a Langendorff apparatus. Intramural transmembrane potentials were recorded adjacent to extracellular measurement sites in the isolated hearts employing a multi-channel fluorescence imaging system and a novel fibre optic probe. The results obtained are consistent with model predictions and reinforce the hypothesis that structural discontinuity may give rise to non-uniform, anisotropic propagation of electrical activation.

The significance of these observations with respect to normal activation, re-entrant arrhythmia and defibrillation will be discussed. Finally, the need for, and progress toward, development of a new generation of computer models of re-entrant arrhythmia that are anatomically realistic and incorporate accurate representations of cellular electrophysiology and include data on the spatial distribution of key transmembrane ion channels will be reviewed.