Cardiomyocyte group architecture and electrical activation pathways in the heart

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Background: Abutting cardiomyocytes form an electrical network that transmits activation and maintains the rhythmic efficiency of heart function. Sufficient structural or electrophysiological disruption to this network can result in conduction disturbance, leading to potentially fatal arrhythmias. The electrophysiological characteristics of isolated cardiomyocytes are well categorized (Luo & Rudy, 1991) and detailed activation sequences have been recorded from the epicardium (Herron *et al.*, 2012) and from the exposed surface of transmural wedge preparations (Libbus & Rosenbaum, 2003). However, such studies only present a partial picture of activation pathways in the intact heart and most have not attempted to explicitly relate electrical recordings to details of the underlying tissue architecture. Combining 3D transmural electrical mapping in large hearts with detailed 3D imaging of cardiomyocyte architecture in both large and small hearts promotes new views of the anatomical basis of electrical activation (Hooks *et al.*, 2007, Caldwell *et al.*, 2009, Rutherford *et al.*, 2012). These views were developed using computer models that link experimental observation to image-based cardiomyocyte group architecture and the biophysics of electrical behaviour, and probe the relationships between the anatomical substrate and electrical activation pathways in the heart.

Methods: Animal models of normal (pig) and infarcted (sheep) hearts were used to map *in vivo* 3D electrical behaviour in the LV free wall and infarct border zone. Animals were anesthetized and maintained with 2-5% halothane (pigs) or isoflurane (sheep) in oxygen using positive pressure ventilation. The heart was exposed *via* a thoracotomy and a 325-electrode array of plunge needles was inserted through the heart wall. All surgical procedures were approved by the Animal Ethics Committee of the University of Auckland. Following the experiment, the hearts were arrested, excised and perfusion fixed. MRI and surface imaging microscopy were used to reconstruct the 3D tissue structure in the vicinity of electrical recordings. Novel image modelling and analysis tools were used to probe correlations between reconstructed 3D electrical signals and the myocyte architecture. Additional high-resolution confocal image sets from rat hearts were used to further analyze myocyte structures, and to provide the basis for computer modelling to unmask key mechanisms governing the progress of electrical activation.

Results: Both *in vivo* and *in silico* studies showed strong scale-dependent relationships between electrical signals and structural features. Three principal conduction velocities and passive electrical conductivities were observed in the pig heart, in the ratio of 4:2:1 aligned with the three principal myocyte architectural axes. Qualitative differences in the spread of local activation between stimulus sites and hearts corresponded to different tissue features, particularly the extent and orientation of clefts between layers of myocytes. In infarcted sheep and rat hearts, results from both *in vivo* and *in silico* studies showed stimulus site-specific delay, block, and non-uniform activation in the border zone. These features were related to rapid changes in the organisation of myocyte tracts. Adjacent to the border zone, the topology of cellular structures and computed conduction velocities were similar to controls. In infarct models, electrical reentry could be induced both *in vivo* and *in silico*.

Conclusions: In both normal and infarcted hearts, electrical activation pathways can be reliably related to myocyte group architectures. These structures are sufficient to explain anisotropic electrical properties. In the infarct border zone, myocyte architecture explains features such as pacing site-specific delay, block, and non-uniform activation, and provides a substrate for electrical reentry.

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