Application of MRI to explore myocardial structural reorganisation accompanying contraction and the influence of this on arrhythmogenesis the normal and post infarct heart

Rapports

Informations projet

MSIA

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Final Report Summary - MSIA (Application of MRI to explore myocardial structural reorganisation accompanying contraction and the influence of this on arrhythmogenesis the normal and post infarct heart.)

Summary of the project objectives:
The structural organization of the myocardial muscle is important for normal electrophysiological activation of the heart muscle and for its normal contraction. The myocardium has a fibre orientation, corresponding to the directionality of the elongated cardiac muscle cells, and a laminar structure/orientation corresponding to the separation of cells into branching sheets 4-6 cells thick. The propagation of the ventricular action potential has recently been shown to be influenced by both fibre orientation and local sheet structure with action potential conduction velocity i) along fibres, ii) within sheets, and iii) across sheets in the ratio 4:2:1, and this has been incorporated in modelling studies. In myocardial contraction mechanics the structural appearance of transmural sheet populations led to development of the ‘sheet sliding hypothesis’: sheets enable systolic ventricular thickening by their sliding across each other during systole, hence relieving shear forces and allowing the large transmural thickness changes through the cardiac cycle. This has been demonstrated by tracking deformation in isolated blocks of fixed tissue, and through comparing rat hearts fixed in systole/diastole using DT-MRI imaging. Although it has been proposed that sheets slide across each other during myocardial thickening during systole, this has not been demonstrated in living tissue, or indeed in live intact hearts, as the spatial resolution required has only recently become technically possible with microscopic MRI in high field strength scanners (9.4T or greater). It is also unknown what influence sheet sliding has on electrophysiological repolarization and arrhythmogenesis. The objective of this study was to investigate the role of myolaminar architecture in electrophysiology and mechanics, particularly as it relates to arrhythmogenesis after myocardial infarction. To do this a model of sheet structure in successive states throughout the cardiac cycle is needed. The overall aim was therefore to explore the role of local myocardial structure, including myocyte fibre and sheet architecture, in cardiac excitation and contraction. My hypothesis was that myocardial systolic thickening is enabled by the sliding of sheets over each other with the laminar architecture serving to limit shear stress. Furthermore, I hypothesized that sheet sliding will have a role in electromechanical feedback24 which will influence the initiation, propagation and termination of arrhythmias. Finally I hypothesize that myolaminar sliding will be absent in infarct scars with consequent large strain in the peri-

infarct region, and that this will have consequences for structural re-organization, the propagation of activation and arrhythmogenesis in the surrounding myocardium.

Description of the work performed and main results achieved:
1. Preliminary studies in CMRI: In order to learn how to carry out in vivo cardiac MRI (CMRI) using the 1.5T MRI scanner I carried out CMRI on existing large animal cardiac studies and analysed the resultant image data. CMRI provided structural, functional and remodelling data which supported the electrophysiological investigations in these studies. Imaging was on two pig models: one of surgical repair of Tetralogy of Fallot (TOF), and the other of a model of cardiac resynchronisation in atrio-ventricular block (BAV). The TOF MRI acquisition and data analysis has led to two co-authored abstracts at a local workshop, one co-authored abstract at a national conference and co-authored accepted abstracts at Heart Rhythm 2014 (San Francisco, USA, one oral presentation, one featured poster. The BAV MRI acquisition and data analysis has led to a co-authored abstract at a local workshop and is likely to lead to a co-authored publication on completion of the study. Additional MRI data analysis training on human CMRI data led to a co-authored abstract at the European Society of Cardiology Conference 2013 and a published co-authored research paper, and a further co-authored research paper accepted subject to minor revisions.

2. Generation and characterisation of a sheep left ventricular infarction model: The generation of this model was a complex multistage process involving many clinicians and researchers. Two methods of infarction induction were explored. The first was balloon occlusion of a branch of the left circumflex coronary artery. The second was ethanol infusion after balloon occlusion of the artery. The latter approach was chosen for future studies based on success rates, mortality rates and uniformity of the resultant infarct. Characterisation included: (i) in vivo electrophysiological mapping (EP); (ii) CMRI; (iii) ex vivo optical electrophysiological mapping; (iv) ex vivo MRI; and, (v) serial histopathology and histopathological data analysis. I led (ii), (iv) and (v) although data from all stages was available to this study, including epicardial activation patterns in vivo and ex vivo from the normal and infarcted sheep heart. This led to one local workshop presentation and further data is under analysis which will likely lead to the submission of a co-authored research paper.

3. Detailed CMRI studies on normal rats, normal sheep and infarcted sheep: Functional data from tagging Cine MRI (SPAMM and CSPAMM) at 1.5T was carried out, along with other protocols. This produced a detailed dataset of cardiac function at maximal achievable spatial and temporal tagging resolution. In the sheep LV pressure was recorded alongside the MRI, and independent PV-loop measurement provided a preload independent measure of cardiac mechanics.

4. Ex vivo high spatial resolution contrast enhanced 9.4 T MRI: These ex vivo images corresponding to the in vivo functional studies described in (3.). Ex vivo high spatial resolution contrast enhanced 9.4 T MRI (HR-MRI) images of rat and sheep hearts in systole and diastole have been obtained for several hearts in the rat and in the sheep (rat: maximum resolution 25 × 25 × 34 μm, sheep: maximum resolution 100 × 100 × 100 μm) in diastole and systole. The same hearts were imaged at 9.4 T using diffusion tensor MRI (DT-MRI). These sheep HR-MRI images are the highest resolution cardiac images of large animal hearts, and the first time that laminar structure of the heart has been directly imaged. An associated negative result was the demonstration that laminar measurement is not possible at 1.5T either in vivo or usefully ex vivo.

5. Development, characterisation and validation of methods for myocardial structural measurement:
Existing image analysis methods where adapted and developed for extracting structural orientations from HR-MRI images (Structure Tensor analysis, ST). The performance of DT-MRI and ST were assessed and their accuracy compared. It was shown that DT-MRI and ST/HR-MRI can be used to accurately measure myocardial fibre orientation but that only ST/HR-MRI is reliable for measurement of myolaminar orientation. This analysis, along with a thorough parameter sensitivity analysis has been submitted to Investigative Radiology as a senior author paper.

Expected final results and their potential impact:
Image analysis and modelling studies are underway using the generated structural and functional image data. Electrophysiological modelling of electrical propagation through left ventricular wedges showed altered activation patterns depending on sheet structure, and also demonstrated the need for refinement of sheet measurement methods. It is expected that this work will lead to a principle author research paper on a method for combining the best features of myocardial structural measurement from DT (fibre) and from ST/HR-MRI data (myolaminar measurement).
The tagging in vivo data is being used in a continuum mechanics modelling framework in order to generate the directions of maximal myocardial shear. These maximal shear directions will be compared to the myolaminar directions derived from HR-MRI. If the predicted maximal shear directions correspond to the myolaminar directions then this will provide strong support for the hypothesis that cardiac myolaminar structure develops in order to minimize intramyocardial shear, and hence provides insights into both the developmental mechanism and physiological-anatomical principles explaining cardiac form. Parallel imaged based modelling of the structure of infarcted hearts will help to explain altered myocardial functioning in diseased hearts. In the long term, these insights into normal cardiac development and function, remodelling of structure in disease, and modified function in disease will help to explain how cardiac mechanical and electrical function are compromised; will assist in the accurate image based diagnosis of myocardial disease, and assist in the understanding of the role of whole organ structure in stretch linked arrhythmogenesis. The research will be taken forward in in a European Association of Cardiovascular Imaging (EACVI) funded research grant in 2014/2015 at the Max Delbrück Center for Molecular Medicine, Berlin and in collaboration with the CARMEN centre in Maastricht.

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