Stephen Gilbert
EACVI Research Grant 2015
Final Report

29.04.2015

Is Myolaminar Architecture Generation Explained by Shear? (IMAGES)

Summary

   This project has 4 phases, as summarized in Table 1. The first 2 phases were of image acquisition, the third phase of image processing and the final phase of image based modelling. Unforeseeable hardware failure (of an ex vivo transmit-receive led to the delay of the ex vivo imaging phase of the study (phase 2). This will be completed by 01.07.2015. This led to delays in phase 3&4 but work is ongoing and will continue over the next year. None-the-less, substantial progress has been made across the 4 phases.

Scientific Progress/Milestones

Task #	Task	Status	Outputs
1	High-Resolution SPAMM in vivo Sheep MRI Imaging and Image analysis (n= 6)	Task Completed	In progress
2	Ex vivo High-Resolution MRI (HR-MRI) and DTI of Sheep Hearts (n = 6)	50% complete *	Annex I
3	Processing and analysis of HR-MRI and DTI data to extract sheetlet orientations	50% complete *	Annex I CP1,PP1
4	Collaborative mechanical modelling of the in vivo SPAMM data	ongoing	ongoing

Table 1

Scientific Results and Conclusions: Phases 1, 2, 3 and 4.

Phase 1: High-Resolution SPAMM in vivo Sheep MRI Imaging
Preliminary analysis and assessment of the tagged MRI data is complete. Further processing and analysis will be required in integration of the data with the structural data from phases 2&3 and ts used in the mechanical modelling study (phase 4)

Phases 2 and 3: Ex vivo Cardiac High-Resolution MRI and Image Processing

Results: A whole heart volume rendering is shown in (Fig. 1A in Annexe 1) which demonstrates the epicardial anatomical detail obtained at 0.08-0.16 mm resolution. Cropping to the apical-posterior ventricles (Fig. 1B,TOP) shows the detail of myocardial sheetlet structure, which was quantified by structure tensor analysis. The left ventricle (LV) myocyte helix angle (αH) and myocyte orientation tracking show the helical transmural profile as previously described from diffusion MRI (Fig. 1C&D, TOP). A transmural lateral LV region of interest (ROI) was quantified, and the sheetlets are clearly discernible and myocyte helix angle (αH) and myocyte orientation tracking have a helical transmural profile (Fig. 1B-D, BOTTOM).

HR-MRI followed by ST has previously been used to measure myocardial laminar and myocyte orientations in rat hearts at 9.4T at 50 μm resolution and was more accurate than diffusion-tensor MRI2. It was uncertain how well this methodology could be scaled up to image large hearts. We

show that the same approach applied to the sheep heart at 9.4T with 80×80×160 μm resolution is adequate to allow quantification of transmural myolaminar and myocyte orientation. The current approach has a long acquisition-time but parallel imaging will be investigated to reduce this.

We therefore presented the first high-spatial resolution ex vivo MRI of myocardial sheetlet structure from the sheep heart, obtained at 9.4T/30cm, using a novel 7 elements transmit/receive array coil. This image data allowed us to reconstruct the ventricular sheetlet and myocyte orientations. The methodology will be applied in the wider study to correlating ex vivo myocardial structure to in vivo excitation and myocardial strain/shear distributions.

Phase 4: mechanical modelling of the in vivo SPAMM data
This work is ongoing in collaboration with the CARMEN group at Maastricht University, but is not yet sufficiently developed to report results or conclusions.

Conference Presentations
CP1 - The outputs from HR-MRI and image processing on a subset of the imaged sheep hearts was accepted as a 30 minute Multimedia e-poster talk in the Myocardial Tissue Differentiation session at the 2015 Toronto ISMRM meeting (the leading international MRI conference) (Annex I). The EACVI contribution to this work was acknowledged in this conference submission and will be acknowledged in the interactive e-poster session.

Publications
Whilst at Berlin I continued research and analysis on rat HR-MRI and image processing on a subset of the imaged sheep hearts. This, along with prior work, led to the publication of the following (senior-author) paper in a leading cardiac imaging Journal. The EACVI contribution to this work was acknowledged in the research paper.
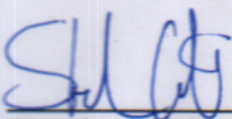
PP1 - Olivier Bernus, Aleksandra Radjenovic, Mark L Trew, Ian J LeGrice, Gregory B Sands, Derek R Magee, Bruce H Smaill and Stephen H Gilbert. Comparison of CMR diffusion tensor imaging and contrast enhanced 3D image intensity approaches to investigation of structural anisotropy in explanted rat hearts, **Journal of Cardiovascular Magnetic Resonance**, In Press.
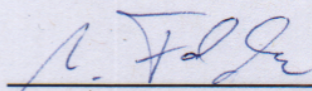
Comments on the Research Programme
I am delighted and honored to have been chosen to receive an EACVI research grant for 2014. I thank the selection committee for selecting my project and particularly for their farsightedness in their choice of this 'basic science' project, which explores the detailed underlying mechanisms of normal cardiac development and mechanical function. The grant has allowed me to carry out research in cardiac structure-function relationships at the Max-Delbrück Centre for Molecular Medicine.

Signed

Grant Winner   **Project Host**

29.04.2015.

Stephen Gilbert PhD   **apl. Prof. Dr Martin Falcke**

Mathematical Cell Physiology
Max Delbrück Center for Molecular Medicine
Berlin, Germany.

Annexe 1

Conference presentations and abstracts of accepted research papers.

Colour accepted poster abstract - following page.

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Measurement and quantification of sheep cardiac myocyte and sheetlet orientation from high-field 80 × 80 × 160 µm contrast-enhanced T1W MRI.

Stephen Henry Gilbert[1], Julie Magat[2], Mark Trew[3], Valery Ozenne[2], Fanny Vaillant[2], Jérôme Naulin[2], Olivier Bernus[2], and Bruno Quesson[2]

[1]Mathematical Cell Physiology, Max Delbrück Center for Molecular Medicine, Berlin, Germany, [2]L'Institut de rythmologie et modélisation cardiaque LIRYC, Pessac, France, [3]Auckland Bioengineering Institute, Auckland, New Zealand

Target audience: MR scientists, clinicians and physiologists interested in high-spatial resolution MR (HR-MRI) and cardiac structure imaging.

Purpose: Imaging of cardiac structure is essential for understanding cardiac electrical and mechanical dysfunction in large animal models of heart disease. These models allow the replication of in vivo clinical imaging alongside high-spatial resolution imaging of explanted organs. Specifically in cardiac disease studies there is a need to know the heart geometry, myocardial myocyte orientation, and myolaminar/sheetlet structure. This is important because myocyte and myolaminar orientation influence electromechanics and are therefore essential for electromechanical computational modelling[1]. It has been demonstrated in rat that high-field high-resolution ex vivo MRI, followed by image quantification can provide this structural information. We describe the hardware requirements and provide the first demonstration of this approach in a sheep heart (~ size of a human heart).

Methods: Sample preparation: A 40 kg female sheep was anaesthetized and underwent a detailed CMR exam, followed by sternal thoracotomy, and euthanasia. The heart was rapidly removed and flushed with cold cardioplegic solution then perfusion fixed for 1.5 hr with 1 L 4% formalin in PBS containing 2 ml Dotarem (gadoterate meglumine, Guerbet, France). Imaging was carried out with the heart removed from formalin and immersed in Fomblin oil. Coil Design: For imaging large animal hearts a volume coil with an inner diameter providing enough space to accommodate the sample and perfusion apparatus is desired, while maintaining homogenous signal intensity and sufficient signal to noise ratio at reception. A prototype coil was developed (by Bruker BioSpin MRI, Ettlingen Germany) through simulation of the B_1 field generated by a 7 elements equally spaced overlapping loop design (100 mm width, 175 mm length) in FDTD (CST Microwave Studio, Darmstadt, Germany). All experiments were performed in a 9.4T magnet with an open bore access of 30cm using this prototype 7 elements transmit/receive array coil. A 3D T_1w FLASH sequence was applied to image the whole heart volume for 29 averages and TE=18ms; TR=50ms; alpha=30°; matrix-size=1380×850×512; voxel-dimensions=80×80×160µm; acquisition-time=97hr; partial-Fourier=1.8. Data treatment: Semi-automated segmentation of the cardiac geometry was carried out using Seg3D (SCI Institute, University of Utah). A structure tensor analysis was then carried out on these images as previously described[2]. The resultant smoothed structure tensor data set had 172×106×64 tensors and voxel dimensions 640×640×1280µm, and was used for myocyte orientation measurement and tracking. Eigenanalysis was used to extract the principal directions from the structure tensor (ST) at each discrete point. The eigenvector corresponding to the largest magnitude eigenvalue (e1) was taken as the laminae normal direction and the eigenvector corresponding to the smallest magnitude eigenvalue was taken as the myocyte direction (e3), following from the orthotropic organization of the myocardium[2]. Myocyte orientation tracking was carried out using Diffusion Toolkit (Centre for Biomedical Imaging, Massachusetts General Hospital, Boston, MA)

Results: A whole heart volume rendering is shown in Fig. 1A which demonstrates the epicardial anatomical detail obtained at 0.08-0.16 mm resolution. Cropping to the apical-posterior ventricles (Fig. 1B,TOP) shows the detail of myocardial sheetlet structure, which was quantified by structure tensor analysis. The left ventricle (LV) myocyte helix angle (α^H) and myocyte orientation tracking show the helical transmural profile as previously described from diffusion MRI (Fig. 1C&D, TOP). A transmural lateral LV region of interest (ROI) is quantified, and the sheetlets are clearly discernable and myocyte helix angle (α^H) and myocyte orientation tracking have a helical transmural profile (Fig. 1B-D, BOTTOM).

Discussion HR-MRI followed by ST has previously been used to measure myocardial laminar and myocyte orientations in rat hearts at 9.4T at 50µm resolution and was more accurate than diffusion-tensor MRI[2]. It was uncertain how well this methodology could be scaled up to image large hearts. We show that the same approach applied to the sheep heart at 9.4T with 80×80×160 µm resolution is adequate to allow quantification of transmural myolaminar and myocyte orientation. The current approach has a long acquisition-time but parallel imaging will be investigated to reduce this.

Conclusion: We present first high-spatial resolution ex vivo MRI of myocardial sheetlet structure from the sheep heart, obtained at 9.4T/30cm, using a novel 7 elements transmit/receive array coil. This image data allowed us to reconstruct the ventricular sheetlet and myocyte orientations. The methodology will be applied in wider studies correlating ex vivo myocardial structure to in vivo excitation and myocardial strain/shear distributions.

References: 1. Trayanova NA et al. Whole-heart modeling: applications to cardiac electrophysiology and electromechanics. Circ Res. 2011;108(1):113-28. 2. Gilbert S H et al, EMBC-Annual International Conference of the IEEE, 2012, 4063-4066.

A – whole sheep heart high-resolution MRI (HR-MRI). **B – D** refer to images of the posterior-apical ventricles (**TOP**) and a region of interest (ROI) in the lateral left-ventricle (**BOTTOM**).
B – high-resolution MRI.
C - myocyte elevation angle (α^H)
D - myocyte orientation tracking

Fig. 1

resolution:
0.08 ×
0.08 ×
0.16 mm

ROI position shown in C, TOP