

21 **CONTRAST ENHANCED MICRO-COMPUTED TOMOGRAPHY RESOLVES THE 3-DIMENSIONAL MORPHOLOGY OF THE CARDIAC CONDUCTION SYSTEM IN MAMMALIAN HEARTS**

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The general anatomy of the cardiac conduction system (CCS) has been known for 100 years, but its complex irregular 3D geometry is not well understood largely because the specialised tissue cannot be easily distinguished from working myocardium. The best anatomical descriptions come from serial sectioning of preparations taken from appropriate areas of the heart. Low X-ray attenuation has formerly ruled out micro-computed tomography (micro-CT) to resolve topology of soft tissue, but incorporation of high molecular weight molecules enhances differential attenuation and allows visualisation of fine detail. Using an iodine based contrast agent, we obtained exquisite high resolution contrast enhanced micro-CT images of cardiac tissue from rat and rabbit in which the three major subdivisions of the CCS can be differentiated from the surrounding contractile myocardium, and visualised in 3D. The sinoatrial node and the associated ring bundle, the atrioventricular conduction axis (including inferior nodal extension and penetrating bundle), His bundle, bundle branches and Purkinje network can be objectively identified by differential attenuation. Purkinje fibres within the ventricles appear both as structures running on the endocardial surface and free running in the luminal cavity. Controversially, analogous structures are present in the atria, mainly on or near to the endocardial surface. Although the current findings are consistent with existing anatomical representations, the new images offer superior resolution and are the first 3D representations of the CCS within intact mammalian hearts. The method promises to improve the anatomical fidelity of computational models designed to understand complex normal and pathological conduction within the heart.

22 **SEMI-AUTOMATIC OEDEMA QUANTIFICATION FROM DIRECT T2 MAP CARDIAC MRI**

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Presenter: Colin Berry

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The jeopardised ischaemic area-at-risk (AAR) is a key prognostic determinant in acute myocardial infarction. Myocardial oedema imaging with T2-weighted cardiac magnetic resonance CMR is validated for imaging the AAR and T2 'mapping' is a new method for AAR imaging with clinical and research potential. We aimed to develop an automated post-processing method that would enable straightforward volumetric quantification of AAR with T2 maps. Our approach retains user input (i.e. clinical judgement) to confirm the presence of oedema on an image which is then subjected to an automated analysis. The new method was tested on 12 acute MI patients who had a CMR within 48 hours of hospital admission. Manual segmentation of the left ventricular wall and oedema were

available for comparison. Left ventricular wall boundaries were delineated automatically by variational level set methods followed by automated detection of myocardial oedema by fitting a Gaussian-Gaussian mixture statistical model. The mean perpendicular distances between automatically detected left ventricular boundaries and corresponding manual delineated boundaries were  $1.8 \pm 0.2$  mm for endocardial boundaries and  $2.3 \pm 0.3$  mm for endocardial boundaries. Dice similarity coefficients for agreement (0=no agreement, 1=perfect agreement) between manual delineation and automated segmentation of the left ventricular wall boundaries and oedema regions were  $0.85 \pm 0.02$  and  $0.74 \pm 0.05$ , respectively. Compared to standard manual approaches, the new semi-automated method for estimating myocardial oedema is straightforward and accurate.

23 **UNCOVERING THE MOLECULAR MECHANISMS OF PATENT FORAMEN OVALE**

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Patent Foramen Ovale (PFO) is a cardiac developmental defect present in ~25% of the general population. It is a major risk factor in cryptogenic stroke and migraine. PFO occurs when the Foramen Ovale (FO), a valve-like passageway in the foetal heart allowing blood to bypass the lungs, fails to fuse shut remaining open into adulthood. Evidence suggests PFO has a genetic predisposition. Genetic variants associated with PFO would serve as biomarkers used for screening high risk individuals. Specific genes that contribute to FO closure are largely unknown. This is attributed to our incomplete understanding of the physiological process of FO closure. To investigate the molecular mechanisms underlying FO closure, gene expression and histological analysis is being performed using rats as a model. For the first time histological analysis of heart tissue sections from rats aged E20 to P7 have uncovered specific contributions of septum primum and secundum to FO closure. Results from immunostaining of marker genes including vimentin, SM alpha-actin and CD-31 have suggested endothelial-to-mesenchymal transition (EndMT) occurs in this process. Based on the fact that patients who have CADASIL, a genetic stroke syndrome caused by NOTCH3 gene mutations, have a high prevalence (80%) of PFO; and that Notch signalling is a critical player in EndMT, immunohistochemical staining of FO regions for genes of the Notch signalling pathway have been carried out. Preliminary results showed specific expression patterns of these genes in FO region. We conclude that FO closure is a process of EndMT with the involvement of Notch signalling.

24 **INITIAL RESULTS OF SIMULTANEOUS PET/MRI EVALUATION OF THE INFARCTED MOUSE HEART**

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**Background** Chronic heart failure (CHF), as a result of acute myocardial infarction (AMI), is currently a leading cause of death worldwide. The direct assessment of novel treatments targeting CHF in vivo however remains difficult. While MRI can reveal cardiac morphology and tissue perfusion through the use of gadolinium (Gd) contrast agents, PET provides information on myocardial function at the molecular level. Here we present preliminary data using a

combined 18FDG PET/MRI imaging system in an AMI mouse model with the aim of acquiring simultaneous morphological and functional data.

**Methods** An open-chest mouse (C57Bl/6J) heart model was utilised in which the left anterior descending coronary artery was occluded for 30 minutes to induce an ischaemic insult. A cardiac MRI with a 4.7T Bruker BioSpec system was performed 24 h after surgery. At 4 weeks post-AMI a second MRI was performed followed by a combined 18FDG PET-MRI investigation using the Cambridge split-magnet system.

**Results** Gd-enhanced MRI at 24 hr reperfusion revealed hyperenhancement of the infarcted region which corresponded to a signal void in the PET image obtained at 4 weeks post-MI. Furthermore, this was associated with a decrease in global ejection fraction as well as left ventricular wall thinning, consistent with the onset of heart failure.

**Conclusion** These preliminary findings demonstrate that the combined PET/MRI imaging system is a powerful tool in studying the pathophysiology of CHF allowing a better understanding of the progressive changes that occur and the direct evaluation of novel therapeutic treatments.

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#### AN MRI COIL DUAL-TUNED BY RF SHIELDING FOR IN-VIVO DETECTION OF FLUORINE LABELLED STEM-CELLS IN A RODENT MODEL OF ACUTE MYOCARDIAL INFARCTION

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Stem-cell therapy holds great promise for treatment of disease. However, optimal stem-cell type, number, route, timing of administration have yet to be quantitatively determined. Non-invasive methods of monitoring cell retention are therefore in demand. Fluorine-MRI offers the facility for unambiguous localisation of fluorine-labelled cells as they migrate in-vivo. We achieve high fluorine sensitivity by simple modification to a standard MRI-coil. We monitored stem-cell retention in a rat model of myocardial infarction (MI), for 13 days after administration of fluorine-labelled stem-cells

**Methods** MRI-coil: 65mm diameter, low-pass birdcage fitted with two RF-shields; 85mm removable, 79mm fixed. Inner shield removal causes the resonant frequency window to shift from proton to fluorine. Labelled cell preparation and administration: cardiac-derived stem-cells were incubated with poly(lactic-co-glycolic acid) (PLGA) nanoparticles containing perfluoro(crown)ether (PFCE) and fluoresceinamine. Five million labelled cells were administered immediately post MI, induced by occlusion of the left descending coronary artery. MRI at 1, 5, 7 and 13 days post MI, using a 7 Tesla magnet. Cardiac-gated gradient-echo cardiac long-axis and short-axis stacks: 1 proton average (Texp~25s), 15 fluorine averages, (Texp~380s) TE=2.9ms, FA=Ernst angle (TR=RRinterval~200ms, T1(PFCE)=1090±15ms in-vivo), FOV=50x50x1.5mm, matrix=128x128.

**Results** In-vivo, fluorine signal was easily located for setup, and high-resolution fluorine images showed signal co-registered with infarction and operation wound. At day 13, hearts were excised for histological verification of MRI findings.

**Conclusion** We demonstrate high proton/fluorine sensitivity using a standard MRI-coil, modified for inductance tuning to fluorine. Labelled cardiac stem-cells were imaged for 13 days post MI. Whole-heart proton and fluorine image stacks of matched resolution were acquired within one-hour scan-time.