04 THE CARDIAC EXTRACELLULAR MATRIX IS REMODELLED DIVERGENTLY WITH AGE IN HEART FAILURE: A ROLE FOR ALTERED COLLAGEN DEGRADATION IN AN OVINE RAPID PACING MODEL

doi:10.1136/heartjnl-2012-302951.004

Presenter: Margaux Horn

MA Horn, HK Graham, KM Dibb & AW Trafford. *Unit of Cardiac Physiology, The University of Manchester, Manchester, UK*

Alterations to the amount, quality and/or distribution of the cardiac extracellular matrix (ECM) are defining features of the structural remodelling which occurs in heart failure (HF). However, whether the ECM remodelling which occurs in the aged failing heart occurs to the same extent as in the young remains to be determined.

HF was instigated in sheep aged either 18 months (young) or >8 years (aged) by rapid ventricular pacing (210 bpm). HF increased LV diameter and reduced fractional shortening (measured by echocardiography) in both young and aged animals (all $P<0.001$), although these changes were more pronounced in the aged ($P<0.05$). LV collagen content measured from picro-sirius red-stained LV sections was altered with HF in an age-dependent manner - with collagen accumulation in young HF ($P<0.001$) and depletion in aged HF ($P<0.05$). Matrix metalloproteinase-2 (MMP-2) activity determined from gelatin zymograms was enhanced with both ageing and in young HF (both $P<0.05$). Protein levels of tissue inhibitor of metalloproteinases (TIMPs) 3 & 4 quantified by immunoblotting were reduced in aged HF only ($P<0.05$). Levels of secreted protein acidic and rich in cysteine (SPARC) were increased in aged hearts compared to young controls ($P<0.05$) whilst serum procollagen type I C-peptide (PICP) was increased in both young failing ($P<0.05$) and aged failing ($P<0.01$) animals, as measured using specific ELISA.

In conclusion, remodelling of the cardiac ECM in HF is age-dependent. Diminished TIMP levels only in aged HF alongside enhanced collagen synthesis in HF provide a potential mechanism for this age-dependent response.

05 NOX2-DERIVED OXIDATIVE STRESS AND BONE MARROW-DERIVED HEMATOPOIETIC STEM CELL DYSFUNCTION IN MIDDLE-AGE OBESITY

doi:10.1136/heartjnl-2012-302951.005

Presenter: Daniel Meijles

DN Meijles, FHMS, J-M Li, FHMS. *University of Surrey, Guildford GU2 7XH*

Systematic oxidative stress is a characteristic of metabolic disorders and cardiovascular diseases associated with middle-age obesity. Bone marrow-derived multi-potent stem cells (BMSC) hold the hope in regenerating damaged tissues; however, the effect of oxidative stress on BMSC function remains unknown. In this study, we investigated the BMSC function in mouse models of middle-age obesity. Littermates of C57BL/J6 wild-type and Nox2 (an O2.–generating enzyme) knockout mice (7 m old, n=15) were fed with high fat diet (HFD, 45% kcal fat, 20% kcal protein and 35% kcal carbohydrate) or normal chow diet (NCD, 12% kcal fat, 28% kcal protein and 60% kcal carbohydrate) for 16 weeks. BMSCs were isolated from mice at 11 m of age. Compared to NCD controls, the numbers of CD133+/VEGFR2+ endothelial progenitor cells (EPC) were significantly decreased (2.2%±0.3 NCD vs. 0.8%±0.5 HFD) in HFD mice. There were significant increases (82±9.2 %) in the levels of O2.- production by HFD BMSC, and this was accompanied with accelerated cell proliferation (160±5.2%), cell cycle progression from G1/G0 phase to S phase, and significant increases in cell apoptosis (6.9±2.5% NCD vs. 29.8±8.2% HFD) as examined by annexin V flow cytometry. Moreover, the levels of PCNA and p53 expression were significantly increased in HFD BMSC. However, all these changes were absent in BMSC isolated from Nox2 knockout mice fed with HFD. In conclusion, an obesity environment activates Nox2 and oxidative stress damages BMSC function and reduces EPC population. Nox2 may present a therapeutic target for the prevention and treatment of obesity-related diseases.

06 DUAL ENERGY CT HAS THE POTENTIAL TO IMPROVE NON-INVASIVE IDENTIFICATION OF NECROTIC CORE

doi:10.1136/heartjnl-2012-302951.006

Presenter: Daniel Obaid

[1]D Obaid, [1]P Calvert, [2]M Goddard, [2]D Gopalan, [1,3]J Rudd, [1,3]M Bennett. *[1]Dept of Cardiovascular Medicine, University of Cambridge. UK; [2]Papworth Hospital NHS Trust. UK; [3]Addenbrookes Hospital NHS trust. UK*

Background CT can classify plaque based on its x-ray attenuation. However, identifying vulnerable plaque is limited by overlap between the attenuation of necrotic core and fibrous plaque. Changes in attenuation of plaque components to x-rays of differing energies may allow better discrimination. We tested whether Dual Energy CT (DECT) (simultaneous image acquisition at two energies) improved identification of necrotic core, both in-vivo and ex-vivo.

Methods 20 patients underwent DECT and 3-vessel Virtual Histology-IVUS (VH-IVUS). Attenuation was sampled in 1088 plaque areas co-registered with VH-IVUS and used to define dual energy indices (changes in attenuation of plaque components at 100 kV and 140kV). 42 plaques were analysed by DECT to determine whether DECT increased sensitivity to detect VH-IVUS defined necrotic core. 10 post-mortem coronary arteries were also examined with DECT prior to histological analysis to determine whether DECT increased sensitivity to detect histologically proven necrotic core.

Results Dual energy indices of necrotic core and fibrous plaque were significantly different (mean: 0.0071 vs. 0.0283, $p<0.05$). Utilising these increased diagnostic accuracy for DECT to detect necrotic core in 87 segments of post-mortem arteries (sensitivity-64%, specificity-96%) compared with single energy CT (sensitivity-54%, specificity-92%). Sensitivity to detect necrotic core was lower in plaques analysed in-vivo due to the impact of temporal resolution on moving coronaries. However, DECT still provided marginal improvements in sensitivity (45%) compared with single energy CT (39%).

Conclusions Dual Energy CT has the potential to improve the differentiation of necrotic core and fibrous plaque allowing more accurate non-invasive identification of vulnerable plaque.

07 SIMULTANEOUS POSITRON EMISSION TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING OF RECEPTORS USING A NOVEL COMBINED PRE-CLINICAL MICROPET/MR SYSTEM

doi:10.1136/heartjnl-2012-302951.007

Presenter: Anthony Davenport

[1]JLE Bird, [2]RC Hawkes, [3]R Manavaki, [2]SJ Sawiak, [2]DJ Williamson, [2]FI Aigbirhio, [4]JHF Rudd, [4]M Bennett, [5]JH Gillard, [7]TA Carpenter, [6]EA Warburton, [1]AP Davenport. *[1]Clinical Pharmacology Unit; [2]Wolfson Brain Imaging Centre; [3]Department of Medicine; [4]Division of Cardiovascular Medicine; [5]Department of Radiology; [6]Department of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital Cambridge CB2 2QQ, UK*

Vascular and cardiac diseases are complex pathologies and preclinical models are required to fully investigate the multifactorial interactions. In vivo imaging techniques are important research tools in quantifying pathogenic mechanisms and positron emission tomography (PET) is an imaging modality which has the chemical