**THE MITOCHONDRIAL PERMEABILITY TRANSITION PORE AS A TARGET FOR CARDIOPROTECTION IN VENTRICULAR CARDIOMYOCYTES HARVESTED FROM PATIENTS WITH OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY**

doi:10.1136/hrt.2010.205781.56

1 P S Crees, 1 S Davidson, 2 S E Harding, 3 M Elliott, 3 M Yellon, 1 J Hauseuolny, 1 The Hatter Cardiovascular Institute, University College London, UK; 2The National Heart and Lung Institute, Imperial College London, UK; 3The Heart Hospital, University College London Hospitals, London, UK

**Rationale**
The opening of the mitochondrial permeability transition pore (mPTP) is a critical determinant of ischaemia-reperfusion injury, and preventing its opening confers powerful cardioprotection in non-diseased myocardium. Whether this cardioprotective effect is present in the setting of hypertrophic cardiomyopathy (HCM) is unknown and is investigated in this study.

**Methodology**
Local UCLH/UCL ethical committee approval had been granted for this study. Human adult ventricular cardiomyocytes were isolated from left ventricular septal tissue, harvested from consenting patients undergoing surgical myectomy for obstructive HCM. The cells were loaded with the fluorescent dye TMRM which localises to the mitochondria, generates oxidative stress within the mitochondria on confocal imaging, resulting in mPTP opening, as indicated by the collapse of the mitochondrial membrane potential. The time taken to induce the loss of mitochondrial membrane potential was used as a measure of mPTP opening sensitivity. Cells were randomised to the following: (1) DMSO 0.01% vehicle control (N=8/group); (2) cells pre-treated with cyclosporin-A (CsA) (0.2 μM) for 15 min (N=7/group); (3) cells pre-treated with atorvastatin (25 μM) (N=7/group).

**Results**
In the control group, mPTP opening was induced after 188.7±22.7 s of oxidative stress, providing evidence for a functional mPTP in the setting of HCM. Furthermore, pretreatment with the known mPTP inhibitor, CsA, and atorvastatin, delayed the onset of mPTP opening by 51%±10% (p<0.001) and 35%±7% (p<0.05), respectively.

**Conclusions**
For the first time in diseased human ventricular myocytes, we have demonstrated that the mPTP is functional and that its opening can be inhibited by cardioprotective agents such as CsA and atorvastatin.

**X-BOX BINDING PROTEIN 1 SPlicing TRiggers AN AUTOPHAGIC SURVIVAL PATHWAY IN ENDOTHELIAL CELLS**

doi:10.1136/hrt.2010.205781.57

Andriana Margariti, Hongling Li, Daniel Martin, Anna Zampetaki, Yanhua Hu, Qingbo Xu, Lingfang Zeng, Cardiovascular Division, King’s College London BHF Centre, London, UK

An initial step in the development of atherosclerosis is endothelial cell dysfunction. Our previous study has shown that sustained activation of X-box binding protein 1 (XBP1) splicing, a key signal transducer in endoplasmic reticulum stress response, leads to endothelial apoptosis and atherosclerosis development (Zeng et al., PNAS 2009). Autophagy is characterised as a survival response as well as a pathway culminating in cell death. In this study, we aimed to investigate whether XBP1 splicing could also activate autophagy in endothelial cells, and its role in the cell survival and apoptosis. XBP1 splicing was induced to human umbilical vein endothelial cells by advenolarin gene transfer, and autophagc vesicle formation was observed 48 and 72 h postinfection. Autophagy gene expression such as Beclin 1, LC3-β, BNIP3, and TMRM, which localises to the mitochondria, generating oxidative stress within the mitochondria on confocal imaging, resulting in mPTP opening, as indicated by the collapse of the mitochondrial membrane potential. The time taken to induce the loss of mPTP opening was used as a measure of mPTP opening sensitivity. Cells were randomised to the following: (1) DMSO 0.01% vehicle control (N=8/group); (2) cells pre-treated with cyclosporin-A (CsA) (0.2 μM) for 15 min (N=7/group); (3) cells pre-treated with atorvastatin (25 μM) (N=7/group).

**Results**
In the control group, mPTP opening was induced after 188.7±22.7 s of oxidative stress, providing evidence for a functional mPTP in the setting of HCM. Furthermore, pretreatment with the known mPTP inhibitor, CsA, and atorvastatin, delayed the onset of mPTP opening by 51%±10% (p<0.001) and 35%±7% (p<0.05), respectively.

**Conclusions**
For the first time in diseased human ventricular myocytes, we have demonstrated that the mPTP is functional and that its opening can be inhibited by cardioprotective agents such as CsA and atorvastatin.

**COMPUTER MOLECULAR MODELLING OF THE P22PHOX PROTEIN STRUCTURAL CHANGES LINKED TO C242T POLYMORPHISM**

doi:10.1136/hrt.2010.205781.59

Daniel Meijles, Brendan J Howlin, Jian-Mei Li. Cardiovascular Research, Faculty of Health and Medical Sciences, University of Surrey, UK

The p22phox is a key component of the cytochrome b558 of the NADPH oxidase (Noox), which by generating reactive oxygen species (ROS) is involved in the pathogenesis of cardiovascular disease. A p22phox polymorphism (C242T) has been found to reduce oxidative stress in the cardiovascular system and is negatively associated with subclinical atherosclerosis. Prediction of subclinical atherosclerosis was improved by comprehensive metabolic profiling. The findings substantiate developments towards the use of multi-metabolic risk phenotypes in cardiovascular risk assessment.

**QUANTITATIVE METABOLIC PROFILING OF SUBCLINICAL ATHEROSCLEROSIS BY SERUM NMR METABONOMICS**

doi:10.1136/hrt.2010.205781.58

1 T P Wörtz, 1 P Soninen, 1 A J Kangas, 2 C G Magnussen, 1 J H Raikko, 4 V P Makinen, 1 P Groop, 6 K Thomson, 6 M J Savolainen, 7 M Junaola, 1 J Vikan, 1 M Kähninen, 1 P Lehtimäki, 2 O T Raitakari, 1 M Ala-Korpela. 1Computational Medicine, University of Oulu, Finland; 2Cardiovascular Risk in Young Finns study group, Turku & Tampere University Hospitals, Finland; 3Epidemiology and Public Health, Imperial College, UK; 4Folkhålsan Research Center, Finland

**Objective**
To determine associations of systemic metabolites with subclinical atherosclerosis.

**Methods**
4407 serum samples were measured by nuclear magnetic resonance (NMR) spectroscopy from the Cardiovascular Risk in Young Finns Study, and carotid intima-media thickness (IMT) was assessed by ultrasound. Numerous lipoprotein lipids subclasses as well as low-molecular-weight metabolites were quantified from the NMR data.

**Results**
In these young adults (aged 24–45 years) data-driven analysis using self-organising maps showed distinct metabolic phenotypes associated with elevated IMT. The phenotypes were characterised by varying combinations of metabolic disturbances including elevated very-low-density lipoprotein (VLDL) and LDL subclasses, but also several low-molecular-weight metabolites. Results for 6-year incidence of high carotid IMT and IMT progression as shown by discrimination and reclassification will also be discussed. **Conclusion**
The study showed different metabolic phenotypes inherently associated with subclinical atherosclerosis. Prediction of subclinical atherosclerosis was improved by comprehensive metabolic profiling. The findings substantiate developments towards the use of multi-metabolic risk phenotypes in cardiovascular risk assessment.