and β²–galactosidase activity. However, these responses were absent or significantly reduced in endothelial cells isolated from Nox2 knockout mice. In conclusion, metabolic disorders in particular hyperglycaemia and insulin resistance play an important role in mediating Nox2 activation and oxidative stress in multiple organs in ageing. Nox2 is involved in normal ageing process-associated vascular inflammation and oxidative damage of endothelial dysfunction.

154 MYOCARDIAL NOX2 ACTIVITY REGULATES ATRIAL FIBRILLATION SUSCEPTIBILITY

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Background Gp91-containing NADPH oxidases (NOX2) are a significant source of reactive oxygen species (ROS) in the human atrial myocardium. An increase in NOX2 activity accompanies atrial fibrillation (AF) induction and electrical remodelling in animal models and predicts incident AF in humans; however, whether an increase in atrial NOX2 activity is necessary to create a substrate for AF remains to be demonstrated. The purpose of this study is to determine whether an increase in NOX2-derived ROS directly contributes to the development of AF and to identify the molecular changes that occur downstream of NOX2 activation in atrial myocytes.

Methods and Results Mice with myocardial NOX2 overexpression (NOX2-Tg) showed a 2-fold increase in NADPH-stimulated superoxide production (2-hydroxyethidium by HPLC) in both the left and right atria, without any other electrophysiological or structural abnormalities (assessed by surface ECG and echocardiography); however, AF susceptibility assessed *in vivo* by transesophageal pacing was significantly higher in NOX2-Tg mice compared with their wild-type (WT) littermate controls (AF probability: 16.9±1.8% vs. 10.2±1.6% respectively, n=25–26/genotype, $p<0.01$). Moreover, oral supplementation with atorvastatin (30 mg/kg/day), an inhibitor of NOX2 activity, substantially reduced atrial NADPH-stimulated ROS and AF susceptibility in NOX2-Tg mice. *Ex vivo* high-resolution optical mapping of di-4-ANEPPS-stained atrial preparations revealed no differences in the action potential duration of left and right atria of NOX2-Tg mice compared to controls, suggesting that electrical arrhythmogenic remodelling does not occur with NOX2 overexpression. However, abnormalities in intracellular Ca^{2+} handling have also been linked to AF; intriguingly, western blot analyses of atrial tissues revealed a 28% reduction (n=11–23/genotype, $p=0.0032$ with un-paired students t-test) in the phosphorylation status of the ryanodine receptor (RyR) at Ser2814 in the right, but not the left atria of NOX2-Tg mice. Our ongoing experiments are now aimed at determining whether NOX2-derived ROS alters diastolic calcium leak from the sarcoplasmic reticulum in isolated atrial myocytes due to altered RyR gating.

Conclusions Myocardial NOX2 overexpression and related increase in NADPH-stimulated ROS production are associated with increased AF susceptibility *in vivo* and reduced RyR phosphorylation at Ser2814. These findings suggest increased NOX2 ROS may promote arrhythmogenesis by modulating atrial calcium handling.

155 HIGHER IGM ANTI OXIDISED LDL ANTIBODIES POINT TO FAVOURABLE PLAQUE CHARACTERISTICS AS DETERMINED BY RADIO FREQUENCY INTRAVASCULAR ULTRASOUND (RF-IVUS) AND NEAR INFRARED SPECTROSCOPY (NIRS) IN THE INTEGRATED IMAGING AND BIOMARKER STUDY 3 (IBIS-3)

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Background Malondialdehyde (MDA)-LDL is one of the main oxidation products involved in atherosclerosis pathogenesis. IgM antibodies against MDA-LDL have been generally regarded as protecting from atherosclerosis. In contrast, the role of IgG antibodies is less clear. How antibody levels relate to coronary atherosclerosis plaque characteristics still needs to be determined.

Hypothesis We tested the hypothesis that low IgM anti-MDA antibody levels in serum are associated with plaques with larger lipid-laden necrotic cores.

Method IBIS-3 was a prospective cohort study that was designed to determine the ability of rosuvastatin to decrease necrotic core volume in coronary atherosclerosis. Patients undergoing coronary artery grafting or percutaneous intervention for (un)stable angina pectoris or myocardial infarction were eligible. After the standard procedure, radiofrequency intravascular ultrasound (RF-IVUS) and near-infrared spectroscopy (NIRS) measurements were performed in a non-culprit coronary artery with a diameter stenosis<50%. After a median of 386 days of high dose rosuvastatin treatment, imaging was repeated on the same segment. Antibodies against MDA-LDL, as well as total serum IgM and IgG, were measured by ELISA. Associations between antibodies and the RF-IVUS and NIRS parameters were assessed using linear regression models with quartiles as independent variables and with further adjustments for age, sex, diabetes, smoking, LDL and HDL cholesterol and previous use of statins.

Results A total of 143 patients of the included patients had both blood samples and RF-IVUS measurements available, and NIRS was also performed on 90 of these. Mean age was 59.6 (9.0) years (84.6% male) and 94.4% were already on a regular statin before inclusion. At baseline, IgM anti MDA-LDL antibody levels had a strong independent inverse relationship with lesional necrotic core volume ($p=0.027$) and percentage ($p=0.011$) as well as with lipid core burden index (LCBI) ($p=0.024$) in the worst 4 mm segment. This relationship was partially dependent on total serum IgM, as higher IgM levels also reflected a favourable necrotic core percentage on RF-IVUS. There was no correlation between any imaging parameter and IgG antibodies, total serum IgG, HDL-cholesterol or LDL-cholesterol. Although total atheroma burden increased over one year, there was no change in necrotic core volume.