KO hearts develop significantly larger infarctions following lethal ischaemia and reperfusion (25.1±1.97% in PINK1+/+ hearts vs 38.9±3.42% ($p<0.01$) and 51.5±4.3% ($p<0.001$) in PINK1+/- and PINK1−/− hearts, respectively). Interestingly, electron microscopic images showed significantly more vacuole-like structures that contained cellular material (indicative of autophagy) in PINK1−/− hearts. We further observed that PINK1−/− hearts had significantly more Beclin1 and total LC3b than hearts from PINK1+/+ littermate controls (Beclin1: 0.674±0.065 in PINK1+/+ vs 0.85±0.019 in PINK1−/− hearts, $p<0.05$) total LC3b: 0.946±0.139 in PINK1+/+ vs 1.445±0.141 in PINK1−/− hearts, $p<0.05$; values are in arbitrary units of densitometry). In conclusion, our results suggest that during ischaemic-reperfusion PINK1 acts as an endogenous protective kinase with the regulation of mitophagy being a possible mechanism of its protection.

BAS/BSCR16 TIME-DEPENDENT CHANGES IN ATRIAL NITRIC OXIDE-REDOX BALANCE IN ATRIAL FIBRILLATION: TRANSLATIONAL RESEARCH (FROM GOATS TO HUMANS)

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Rationale Oxidative stress has an important role in atrial fibrillation (AF)-induced myocardial remodelling, suggesting that specific oxidases may represent a novel therapeutic target in AF. Here we evaluated how the duration of AF affects the level, sources and localisation of superoxide.

Results and methods Our previous work in patients with predominantly paroxysmal AF showed that increased superoxide was produced by NOX2/NADPH oxidase. Here, in patients with permanent AF (n=26) versus matched controls in sinus rhythm (n=53), increased superoxide (assessed by lucigenin-enhanced chemiluminescence and 2-hydroxyethidum detection) was maintained by mitochondrial oxidases and 'uncoupled' nitric oxide synthase (NOS), but not NOX2/NADPH oxidase; although NOX4/NADPH oxidase was upregulated (real-time RT-PCR). Immunoblotting revealed increased protein expression of the mitochondrial complexes I–V and mitochondrial antioxidant peroxiredoxin-3; NOS 'uncoupling' was associated with reduced tetrahydropterin by 40% (BH4, HPLC).In the goat, after 14 days of AF, NADPH oxidase activity and protein expression were increased in the left atrium (LA). After 6 months of AF, superoxide release was doubled in both atria and originated from mitochondrial oxidases and 'uncoupled' NOS, which was associated with ipsilaterally reduced BH4 and increased arginase activity. Manganese superoxide dismutase was reduced by 50% at this stage.

Conclusion Activation of LA NOX2/NADPH oxidase occurs early in AF and is transient, since mitochondrial oxidases and 'uncoupled' NOS account for the increased superoxide production in permanent AF in both models. This suggests that NADPH oxidases may be a valuable target for 'upstream' treatment in short-term AF, but not once AF is established.

BAS/BSCR17 MYOCARDIAL XANTHINE OXIDASE REGULATES BASAL INOTROPY IN MURINE LEFT VENTRICULAR MYOCYTES

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Xanthine oxidase (XO) is a major source of reactive oxygen species in the cardiovascular system. Enhanced XO activity in the failing myocardium has been associated with a reduction in inotropy; however, whether this association is causal remains to be established. To test this hypothesis, the effect of XO inhibition (oxypurinol, 100 μmol/l and allopurinol, 100 μmol/l) or activation (xanthine, 100 or 500 μmol/l) on cell shortening (3 Hz, 35°) was evaluated in left ventricular (LV) myocytes isolated from C56BL/6–129j mice. Similarly, LV superoxide production in the absence and presence of inhibitors of XO, NADPH oxidases (apocynin, 100 μmol/l) or nitric oxide synthases (LNAME, 1 μmol/l) was measured by lucigenin (5 μmol/l)-enhanced chemiluminescence. Oxypurinol and allopurinol significantly suppressed basal superoxide production and cell shortening (by about 20%), whereas xanthine caused a dose-dependent increase in cell shortening and superoxide production. In contrast, apocynin had no effect on superoxide release or cell shortening. Taken together, our findings indicate that superoxide production by XO exerts a tonic positive inotropic effect on murine LV myocytes, suggesting that the increase in XO activity in heart failure may be, at least in part, adaptive.

BAS/BSCR18 PROTECTION FROM DEVELOPMENT OF OBESITY IN HIGH-FAT DIET FED RATS IS ASSOCIATED WITH PRESERVATION OF THE ANTICONTRACTILE FUNCTION OF PERIVASCULAR ADIPOSE TISSUE

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Introduction In health, perivascular adipose tissue (PVAT) has an anticontractile function on adjacent small arteries. We have recently shown that adipocyte hypoxia and inflammation in obesity attenuates PVAT anticontractile function. In animals, PVAT function has only been examined in genetic models of obesity, which are rare in clinical practice.

Methods 11 Sprague–Dawley rats were fed a high-fat diet (HF; n=11) over 15–18 weeks. Seven control animals received a normal diet. Weight and blood pressure were monitored. The HF rats were split into two groups: (a) diet-induced obese (DIO; n=6): significantly gained weight after a 10-week period, and diet resistant (DR; n=5): weight comparable to control group. Mesenteric arteries were studied using wire myography with construction of cumulative dose responses to noradrenaline, with and without PVAT intact.

Results The weight and systolic blood pressure for DIO were significantly increased compared with the controls (systolic BP: control: 124%±4; DR: 138%±8; DIO: 150%±3 $p<0.05$). The contractile responses of vessels with intact PVAT were significantly different from vessels without PVAT in control ($p<0.001$—multiple ANOVA) and DR ($p=0.001$—multiple ANOVA) groups. In DIO, the dose–response curves for vessels with intact PVAT and without PVAT were not significantly different ($p=0.210$—multiple ANOVA).

Conclusion The anticontractile function of PVAT was preserved in DR, but partially lost in DIO. This suggests that weight gain rather than diet itself initiates PVAT damage, which is associated with hypertension. This is the first animal model of environmental obesity in which PVAT function has been studied.

BAS/BSCR19 VISUALISING INFLAMED ATHEROSCLEROTIC PLAQUES: MOLECULAR IMAGING USING MRI AND TARGETED ULTRASMALL SUPERPARAMAGNETIC PARTICLES OF IRON OXIDE

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Introduction There are currently no clinical imaging techniques available to assess the degree of inflammation associated with