133 patients have been tested, including newly diagnosed cardiac cases, patients negative for other cardiac gene testing, and patients who have phenotype/genotype incompatibility where contribution of more than one gene is suspected. 41/133 (30%) patients have at least one potentially pathogenic variant. 22 patients have multiple plausible variants.

We present data from the cardiac cohort tested to date and cases illustrating the utility and complexity of gene panel testing for cardiac disease including; 1) A paediatric patient with Left Ventricular Non-Compaction (LVNC), dilated aortic root and sinus brachycardia heterozygous (on the PC 71 gene panel) for a novel *TMEM43* variant c.994A>G, p.(Thr332Ala) of unknown clinical significance. Further testing using a bespoke 138 gene cardiac panel from the Focused Exome detected a novel splice variant in the *HCN4* gene associated with LVNC and primary sinus brachycardia (Milano *et al*, 2014). This patient's mother who has aortic dilation and regurgitation was heterozygous for the *TMEM43* variant and the half-brother who also has dilated aortic root and LVNC did not carry either variant. 2) A large Dilated Cardiomyopathy (DCM) family with variable severity between family members, one affected cousin was heterozygous for a variant of uncertain significance in *MYBPC3* c.3384G>C, p.(Glu1128Asp) and another affected cousin heterozygous for a truncating *TTN* variant, c.89244del, p.(Phe29748Leufs*7). Further family studies are ongoing.

Detailed phenotypic assessment (using a clinical proforma) has been shown to increase diagnostic yield in patients with complex cardiac disease.

REFERENCE

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211 NON-CANONICAL NF-ÎšB SIGNALLING PROMOTES ENDOTHELIAL PROLIFERATION IN RESPONSE TO LOW WALL SHEAR STRESS

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Introduction Atherosclerotic plaques are predominantly localised to bends and branches of arteries. In contrast to straight regions where the blood exerts unidirectional high frictional drag, known as wall shear stress (WSS) on endothelial cells (ECs), at atheroprone sites ECs are exposed to complex multidirectional low WSS. These forces cause altered gene expression in ECs, leading to enhanced proliferation, apoptosis, inflammation and lesion development. While the canonical NF-Î¹B pathway has been well studied in early atherogenesis, the non-canonical NF-Î¹B pathwayâ€ " regulated by proteasomal processing of the precursor p100 to active p52â€ "has not been examined directly in this context.

Methods and results To determine the effect of WSS on non-canonical NF-Î¹B activity, human umbilical vein ECs (HUVECs) were exposed to 72 h of low or high WSS and non-canonical NF-Î¹B expression was analysed by Western blotting. Levels of p100, p52, RelB and IKKÎ ± were elevated under low WSS in comparison to high WSS. In addition, exposure to a known non-canonical NF-Î¹B stimulus CD40L revealed exaggerated pathway activity under low WSS. Depletion of p100 by siRNA resulted in a decrease in proliferation in response to low WSS, measured by Western blotting for Ki67 and staining for PCNA.

Conclusions The non-canonical NF-Î¹B pathway is primed by low WSS for enhanced activation in response to physiological stimuli. p100/p52 promoted EC proliferation under low WSS conditions, indicating that this pathway could be targeted in the prevention or treatment of atherosclerosis.

212 ASSESSMENT OF LEFT VENTRICULAR CONTRACTILE RESERVE IN PATIENTS WITH SEVERE SYMPTOMATIC AORTIC STENOSIS AND PRESERVED EJECTION FRACTION

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Introduction Transcatheter aortic valve implantation (TAVI) has become the standard of care for high risk patients. Perioperative deterioration of left ventricular (LV) contractile function was previously demonstrated after surgical aortic valve replacement. Moreover, there is evidence to suggest that patients with severe LV hypertrophy have diminished contractile reserve. We sought to compare the contractile reserve of aortic stenosis (AS) patients to control and heart failure groups utilising a gold standard load-independent technique.

Methods Patients undergoing TAVI under general anesthesia (AS) and control (Ctrl) and heart failure (HF) patients undergoing diagnostic coronary angiography were recruited for invasive pressure-volume loop studies. We measured systolic indices at rest and followed that by assessment of force-frequency relations with atrial pacing. After correction to body surface area, linear mixed model analysis and Friedman test were used to identify differences. Mean values and standard errors are reported.

Results Sixteen (16) patients were in AS group *Vs* 15 and 12 in Ctrl and HF groups (age in years 84.3 ± 1.5, *Vs* 59.4 ± 2.2 and 48.5 ± 4.2, $p < 0.001$; male 8 (50%), *Vs* 5 (33%) and 8 (66%), $p = 0.46$, respectively).

At rest, ejection fraction (EF) for AS group was 66% ± 4 *Vs* 64% ± 4, 42% ± 5 for Ctrl and HF respectively ($p = 0.006$). The maximum first derivative of LV pressure (dP/dt_{max}) was 1097 ± 77mmHg/s *Vs* 1327 ± 63 and 1034 ± 58, $p = 0.017$. The load-independent parameters included end-systolic pressure volume relationship (ESPVR) for AS 1.85 ± 0.25 mmHg/ml *Vs* 1.95 ± 0.35, 1.06 ± 0.18 ($p = 0.14$), Starling Contractile Index (SCI) for AS 7.06 ± 0.9 mmHg/ml/s *Vs* 7.34 ± 0.9, 4.77 ± 0.6 ($p = 0.124$) and Preload Recruitable Stroke Work (PRSW) for AS 40 ± 4.2 mmHg/ml *Vs* 39.6 ± 4.9, 22 ± 3.7 for Ctrl and HF respectively ($p = 0.03$).

With incremental pacing, dP/dt_{max} was biphasic in AS patients (1097 to 1300 then 1084, $p = 0.24$) but upsloping in Ctrl cohort (1327 to 1778, $p = 0.045$) and flat in HF (1034 to 1356, $p = 0.19$) (Figure 1). ESPVR declined steadily in AS patients with incremental pacing unlike the other 2 groups however the changes did not reach statistical significance. SCI response was biphasic in AS (7.7 to 11.9 then 8.1, $p = 0.18$), upsloping in both Ctrl group (5.6 to 11, $p < 0.01$) and HF cohort (4.5 to 6.1, $p = 0.006$) (Figure 2).