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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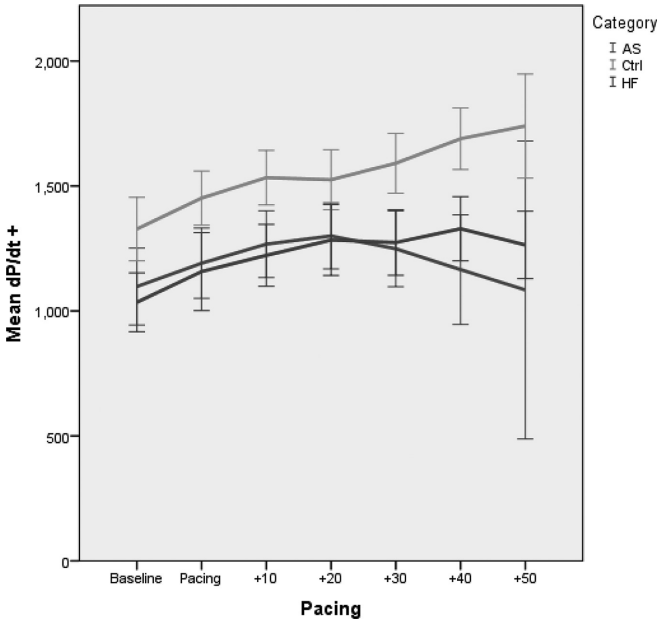
Introduction Transcatheter aortic valve implantation (TAVI) has become the standard of care for high risk patients. Perioperative deterioration of left ventricular (LV) contractile function was previously demonstrated after surgical aortic valve replacement. Moreover, there is evidence to suggest that 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).



Abstract 212 Figure 1 dP/dt+ change with incremental pacing

PRSW remained unchanged in all categories with incremental pacing.

Conclusion These data suggest that aortic stenosis patients with preserved EF have diminished contractile reserve, especially during increased heart rate, and may explain why some of these patients have an unfavorable clinical course post TAVI.

213 THIRD CORONARY ARTERY – AN AUTOPSY STUDY

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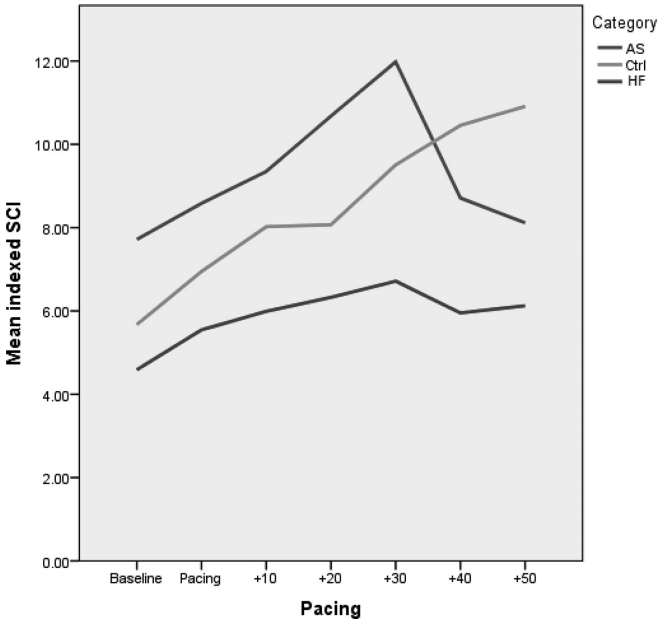
Brief Introduction Anatomy and functionality of the coronary circulation have been of interest to physicians ever since it emerged that mammalian hearts have their own blood supply. If asked how many coronary arteries the normal heart has, most of the medical students (and many practitioners) would answer 'TWO'. However, the frequent presence of two right coronary artery roots is not generally well appreciated, even though it has been evident to anatomists and cardiac surgeons for centuries. The human heart is in most cases vascularized by two coronary arteries, the right and the left coronary artery. Supernumerary coronary artery, which arises independently from the right aortic sinus and passes through sub-epicardial adipose tissue of pulmonary conus and anterior side of the right ventricle; is called Third coronary artery. The Third coronary artery (TCA) is a direct branch from the Right Aortic Sinus (RAS) without any observable common trunk with the Right Coronary Artery (RCA).

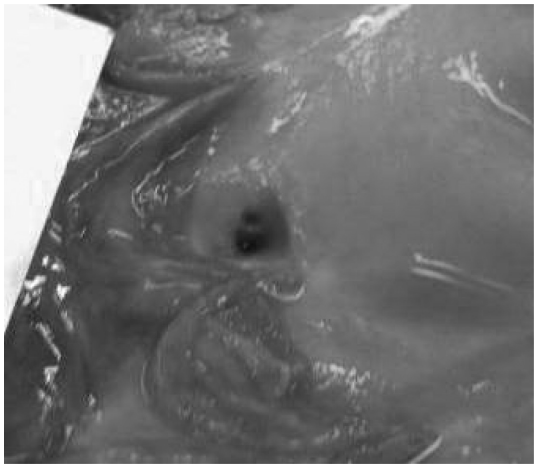


Abstract 212 Figure 2 SCI change with incremental pacing

Methodology This study was conducted at Department of Forensic Medicine and Toxicology, Bangalore Medical College and Research Institute, Bengaluru for a period of 6 months from January 1st 2011 to 30th June 2011. A total number of 1779 autopsy cases were performed during the study period, out of which 550 cases were selected for our study. Specimens with observable cardiac defects and decomposed cases were excluded from the study. The hearts were dissected to display the origins of the right, left and third coronary arteries. The aortic root was split posteriorly to enable a clear view of the RAS with its orifices. With the aid of dissecting lenses, the branches of the TCA were displayed and traced distally to confirm the course, branching and termination.

Results Out of the 550 hearts dissected, Third coronary artery (Figure 1) was present in 184 hearts, which amounts to 33.45%. According to the position of the third coronary artery, 83.15% was in 10â€ ˜clock position. Majority of the Third coronary artery, i.e., 78.8% had an independent course without obvious anastomosis. Multiple orifices (Figure 2) have been seen in 3 individuals. It was observed that among the 95 natural death cases, 32 cases were due to sudden natural death of cardiac origin. In these 32 cases, third coronary was present only in 3 cases.

Conclusion The most suitable term to identify supernumerary artery that arises independently from the right aortic sinus is the Third coronary artery. The present study highlights that the incidence of Third coronary artery is 33.45%. It was observed that among the 95 natural death cases, 32 cases were due to sudden natural death of cardiac origin. In these 32 cases, third coronary artery was present only in 3 cases. It



Abstract 213 Figure 1 Third Coronary Artery