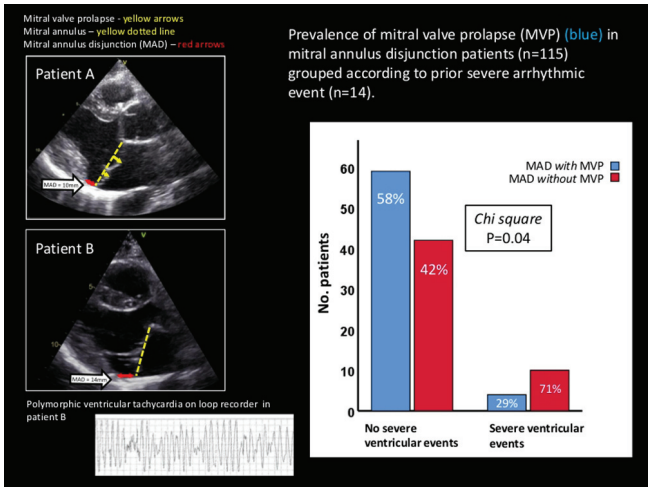
variable logistic regression model including EF, age and MVP, lower EF (Adjusted OR 0.86 (95% CI, 0.77–0.97, p=0.01)) and lower age (Adjusted OR 0.94 (95% CI, 0.89–0.98, p=0.006) remained independent markers for severe arrhythmic events.



MVP in MAD with severe arrhythmic events

Conclusions: Patients with MAD frequently presented with arrhythmic symptoms, and 12% had experienced severe arrhythmic events. MVP was found in only half of the patients with MAD and was not associated with arrhythmic events, indicating MAD itself as an arrhythmogenic entity. In patients with MAD, lower age and EF were markers of severe arrhythmic events.

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P5441
Aortic valve phenotype associated with filamin-A mutations: a comprehensive echocardiographic and outcomes analyses

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Background: Filamin-A (FLNA) mutations has been associated with the development of mitral valve prolapse and a unique features described as a paradoxical restrictive leaflets motion in diastole has been recently described using a comprehensive echocardiographic screening. In addition to the mitral valve dystrophy, polyvalvular diseases have been reported in these patients, especially on the aortic valve.

Purpose: The aim of this study was to perform a comprehensive echocardiographic analysis of the aortic valve (AV) and the proximal aortic root of patients with FLNA mutations, and determine the impact of the aortic disease on outcomes of these population.

Methods: We included in this analysis 253 subjects (37±21 years, 94 men, 76 mutated: FLNA+) in whom we ascertained the genetic status, from 5 FLNA-MVP families. Comprehensive echocardiographic characterization of the aortic valve and the proximal aortic root, including the measurement of the aortic annulus, sinuses of Valsalva, sinotubular junction and ascending aorta, was performed in FLNA+ patients vs control relatives.

Results: Aortic valve alteration was found in 46 subjects (18%) overall, but in 38 (50%) of FLNA+ compared to 8 (5%) FLNA- subjects ($P<0.05$). Out of the 76 FLNA+ patients, 6 (8%) had a bicuspid aortic valve phenotype as opposed to 1 (0.6%) in control relatives (p=0.004). The underlying disease affecting the aortic valve was AV sclerosis, stenosis and AV regurgitation with either prolapse or restricted cusps motion. A restrictive opening of the AV was also observed in some patients. Aortic valve mean gradient was slightly increased in FLNA+ compared with FLNA- subjects (5.7±5.1 vs 4.1±1.9 mmHg, P=0.02) related to stenotic valves in FLNA+. In adults, left ventricular outflow tract diameter tended to be larger in FLNA+ subjects, and sinuses of Valsalva were slightly but significantly larger as compared to control relatives (17.3±2.4 vs 16.2±2.1 mm/m^2; $p<0.05$). The rate of aortic valve-related surgery of FLNA+ subjects was increased (19.4±7.1 vs 0% at 70 year old, $P<0.0001$), especially in male (52.5±17.0 vs 0% at 70 year old, $P<0.0001$). Survival was impaired in FLNA+ male subjects (84.3±8.7% vs 55.9±14.1 at 70 year old, P=0.011).

Conclusion: The FLNA-mutated patients show up more frequently AV disease, in the aspect of bicuspid AV, stenosis, and regurgitation owing to either cusp prolapsed or restrictive motion. This unique features described in this population was associated with worse outcomes in FLNA+ males and should be factored into the management and decision making of these patients.

P5442
Prevalence and predictors of atherosclerotic peripheral arterial obstructive disease in heart valve disease

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Background: Despite witnessing an upsurge in heart valve disease (HVD), the correlation between HVD and atherosclerotic peripheral arterial obstructive disease (PAOD) remains unclear.

Purpose: This study aims to investigate the prevalence and predictors of atherosclerotic PAOD in HVD.

Methods: We examined 245 consecutive patients, 153 with severe aortic valve stenosis (AS), 66 with severe primary mitral valve regurgitation (MR), and 26 with severe aortic valve regurgitation (AR). All patients underwent ultrasound scan of the carotid artery. We evaluated the maximum IMT of the common carotid artery (CCA-IMT). Carotid plaque was defined as a focal region with IMT >1.0 mm by carotid ultrasound. The plaque thickness was measured in the observation-possible area of the common, bulbus, and internal carotid arteries on the right and left sides. We calculated the carotid plaque score by summing all plaque thicknesses for the three segments on both sides. Furthermore, internal carotid artery stenosis (ICAS) was defined as a peak systolic velocity ≥125 cm/s and/or ≥50% reduction in diameter. In addition, we measured the ankle–brachial index (ABI) in each leg using a volume plethysmograph. A result of ≤0.9 was considered a diagnostic of lower-extremity PAOD.

Results: The CCA-IMT and the carotid plaque score were significantly higher in patients with AS than in patients with MR and AR (Figure 1A and B). The presence of ICAS was statistically more frequent in patients with AS than with MR and AR (11.1% vs. 1.5% vs. 3.8%; P=0.038). The ABI was significantly lower in patients with AS than in patients with MR and AR (Figure 1C). In addition, lower-extremity PAOD was present in AS (17.6%) and MR (10.6%) patients but not in AR patients (P=0.037). In this study, the prevalence of PAOD was 15.9% in 245 patients. Patients with both ICAS and lower-extremity PAOD were 2.9%, all of whom were patients with AS. The multivariate analysis revealed that while the presence of AS (OR, 5.6 [1.3–24.9]; P=0.023) was an independent predictor for ICAS, history of coronary artery disease (OR, 4.8 [2.2–10.5]; $P<0.001$) was an independent predictor for lower-extremity PAOD. Of the 245 study patients, 225 patients underwent invasive treatment (aortic valve replacement, 63; TAVI, 79; mitral valve plasty, 45; mitral valve replacement, 15; and aortic valve replacement, 23). Among 225 patients, no patients with ICAS had carotid artery intervention and cerebral infarction during the perioperative phase. However, we experienced only one patient in this study with AS who had cerebral infarction.

Comparison of the CCA-IMT (A), the carotid plaque score (B) and the ABI (C) according to HVDs.

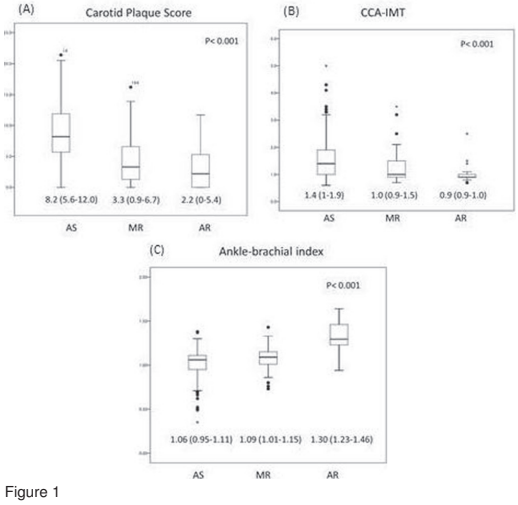

Figure 1

Conclusions: The prevalence of PAOD varies depending on each valvular disease. Routine screening of PAOD for all patients with HVD was inadequate. Individual screening based on atherosclerotic risk factors, especially for patients with severe AS, should be considered. Further studies are warranted to evaluate the clinical impact of coexisting PAOD in patients with HVD for long-term prognosis.

P5443
Association of G allele of CTLA 4 1661 A/G polymorphism with susceptibility and severity of rheumatic heart disease

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Background: Rheumatic heart disease (RHD), a prevalent cause of heart failure in majority of the developing countries, is characterized by progressive and per-

manent valvular lesions. Environmental as well as genetic factors are known to play a notable role in the pathogenesis of RHD. Several single nucleotide polymorphisms (SNPs) in genes that code for inflammatory molecules and contribute to predisposition and manifestation of the disease have been investigated. CTLA-4 gene is found to be co-localized on band q33 of human chromosome 2. It is a co-stimulatory molecule and is expressed on the surface of activated T-cells, and plays a pivotal role in the inhibition of T-cell activation and peripheral tolerance. It is a negative regulator of T-cell activation and alteration of its expression may have a notable effect in immune-mediated diseases. Two SNPs –318 C/T and +49 A/G of CTLA-4 have been studied with respect to RHD; whereas, a third SNP –1661 A/G has been less characterized, although it has been associated with type 1 diabetes mellitus, systemic sclerosis, multiple sclerosis and oral squamous cell carcinoma thus indicating a correlation between this SNP and autoimmune diseases.

Purpose: In this study, we conducted a case-control interpretation to look for any association of four SNPs namely, –1661 A/G, +49 A/G, –318 C/T of CTLA-4 and –308 C/T of TNF-α with RHD.

Methods:. Through the outpatient clinic, a total of 83 RHD North-Indian patients and 291 healthy unrelated North-Indian controls were recruited, and their demographic and clinical profile was recorded. Genotyping was performed using SNaPshot ddNTP Primer Extension PCR.

Results: Among the 4 SNPs, –1661 A/G emerged as significant with respect to disease severity with the minor G allele being less frequent in RHD patients compared to the controls ($p<0.05$). Importantly, segregation of patients on the basis of severity i.e. MVL (Mitral Valve Lesion) and CVL (Combined Valve Lesion) revealed that the G allele depleted as the disease progressed to CVL ($p<0.05$). Patients in the middle age group of 31–45 years were significantly more susceptible ($p<0.046$), whereas the number of patients in the upper age group of 46–60 was significantly less to achieve statistical significance. Also, a significant difference was observed in the dominant genotype –1661 A/G frequency of CTLA-4 ($p=0.049$) as well as the additive model's G allele frequency ($p=0.040$) in females.

Conclusion: Present study thus reports the association of depletion of G allele of CTLA-4 –1661 A/G SNP with susceptibility of RHD. It also explains the higher susceptibility of females for RHD. Moreover, it also correlates with the severity of disease in the form of multivalvular involvement.

P5444
Association between Valvuloarterial Impedance and Cardiac Sympathetic Nerve Activity in Patients with Severe Aortic Stenosis

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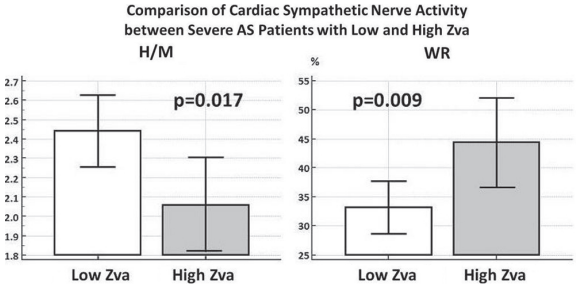
Background: Left ventricular (LV) global afterload is estimated by valvuloarterial impedance (Zva), and considered to be severely increased when Zva is $\geq$5 mm Hg/mL/m^2 in patients with aortic stenosis (AS). Cardiac sympathetic nerve activity evaluated by Iodine-123 meta-iodobenzylguanidine (MIBG) has been reported to be associated with prognosis in patients with heart failure.

Hypothesis: Zva is associated with cardiac sympathetic nerve activity in patients with severe AS.

Methods: We prospectively studied 74 consecutive patients (age 82±7 years, 26 males, LV ejection fraction (EF) 60±9%) with severe AS (mean pressure gradient (MPG) 54±19 mm Hg; aortic valve area (AVA) 0.74±0.18cm^2). Zva was calculated as MPG + systolic blood pressure (SBP) / stroke volume index (SVI). All patients were divided into two groups by Zva value 5 mm Hg/mL/m^2; low Zva (n=52) and high Zva (n=22). LV diastolic function was assessed by the ratio of transmitral peak E-wave velocity to peak A-wave velocity (E/A) and the deceleration time of E-wave (DT) using echocardiography. Cardiac sympathetic nerve activity was assessed by delayed heart-to-mediastinum ratio (H/M) and washout rate (WR) using MIBG.

Results: Age, prevalence of diabetes, chronic kidney disease, atrial fibrillation, symptoms, E/A, DT, and EF were not different between 2 groups. However, significant differences were found in MPG, AVA, SBP, SVI, H/M and WR between 2 groups (all $p<0.05$). Then, Zva was significantly correlated with H/M and WR ($p=0.017$, $p=0.005$, respectively).



Conclusions: LV global afterload was significantly associated with cardiac sympathetic nerve activity in patients with severe AS. This results may explain the importance of Zva as prognostic factor in AS.

P5445
Echocardiographic screening for rheumatic heart disease; the potential for misclassification of "borderline" cases

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Introduction: Echocardiographic screening is an important strategy to identify individuals with asymptomatic rheumatic heart disease (RHD). The 2015 World Heart Federation (WHF) criteria are the current gold standard for echocardiographic case detection. The criteria rely on Doppler echocardiography to identify pathological regurgitation through grading severity rather than identifying the underlying mechanism. The overarching hypothesis being that "pathological" mitral regurgitation (MR) in regions at high risk for RHD is likely to represent true RHD. This presupposes that no alternative common causes of "WHF pathological" MR exist in the general population.

Our initial RHD screening experience in a high-risk cohort (Echo in Africa Project) has highlighted a normal variant of the posterior mitral valve leaflet (PMVL), so called "inter-scallop separations" (ISS), that can be associated with "WHF pathological" MR. These slit-like separations between PMVL scallops are well described in anatomical texts with marked heterogeneity relating to their location, number and depth of excursion into the PMVL (figure 1). Their role in RHD screening studies remains unexplored.

Purpose: To test the hypothesis that PMVL ISS are responsible for a significant proportion of "WHF pathological" MR identified in the WHF borderline RHD category.

Methods: Secondary schoolchildren (aged 13–18) underwent echocardiographic screening in a tailored examination cubicle at their school. Screened cases were classified according to the current WHF criteria. ISS-related MR was defined as MR seen to originate through a slit-like defect between adjacent PMVL scallops.

Results: 571 participants were screened in this study. Comprehensive echocardiography identified 4 cases of mitral valve prolapse, 5 cases of WHF "definite" RHD and 25 cases of WHF "borderline" RHD. Of these "borderline" cases, the mechanism of MR was indeterminate in 8 (32%) and in 17 (68%) were attributable to an ISS. No rheumatic morphological features were present in these cases.

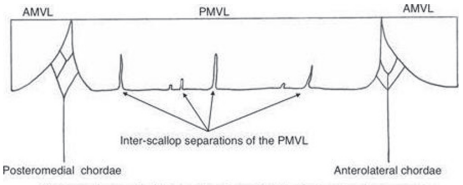

Figure 1: Anatomical illustration of a splayed mitral valve demonstrating heterogeneity of the size, depth and location of inter-scallop separations(ISS) (PMVL: posterior mitral valve leaflet, AMVL: anterior mitral valve leaflet)

Conclusion: ISS appears to be a common cause of "WHF pathological" MR in RHD high-risk populations and should be excluded by careful echocardiographic evaluation to avoid misclassification.

P5446
Profiling DNA methylation patterns in human aortic and mitral valves

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Background: Valve Interstitial cells play a major role in normal physiology and in the molecular and cellular pathogenesis of valvular diseases. These cells are tightly regulated by a variety of mechanisms including genetic and epigenetic factors, such DNA methylation. Methylation fingerprints from normal aortic and normal human mitral VICs are not well studied.

Methods: Tissue from 7 paired normal human aortic valves (no sample data) and mitral valves (6 males, 1 female, mean age= 59.4 yrs, age range 42–84 yrs) was de-endothelialised using collagenase, washed and frozen immediately. Tissue lysates were separately subjected to DNA isolation, bisulphite conversion, and multiplex Next generation sequencing on an Illumina HiSeq2500. Quality control on the raw reads was done using FASTQC version 0.10.1. After trimming via Trim Galore version 0.3.7, the trimmed reads were mapped to human genome sequence (hg19) using Bismark, a methylation aware mapper. An enrichment analysis using Panther version 11 was performed on genes with differentially methylated regulatory elements to functionally classify them based on GO terms.

Results: Different methylation patterns were encountered in aortic and mitral valves involving several relevant gene clusters that play major roles in processes that affect essential valve functions. These genes include ECM genes such as class L phosphatidylinositol glycan anchor biosynthesis gene (PIGL) and zona pellucida glycoprotein 1 (ZP1). These genes encode for proteins that are essential for valve movement, protein secretion and heart morphogenesis. Also, ma-