Immunohistochemical Study on the Pathogenesis of Human Calcific Aortic Valve Disease

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Objective: Investigation of cell-signaling pathways that may participate in pathogenesis of aortic valve calcification. Material and Methods: Formalin-fixed, paraffin-embedded human calcified aortic valves (CAVs) (n = 17) were used from patients undergoing valve replacement for aortic stenosis. Formalin-fixed, paraffin-embedded normal aortic valves (n = 6) obtained at autopsy were used as controls. Immunohistochemistry was performed using antibodies directed against CD68, CD8, SM-ACTIN, OSTEOCALCIN, RANKL, RANK and OPG. Results: In normal valves were identified scattered SMA and CD68 positive cells. OPG intense immunostaining cells were seen in all layers of normal valves. However, no OSTEOCALCIN, RANK, RANKL or CD8 immunopositive cells were noticed. In myxomatous stromal valve areas were seen SMA positive cells, an inflammatory infiltrate composed of macrophages and T cells and weak to absent RANKL, RANK expression. In CAVs, clusters or isolated macrophages and numerous SMA immunopositive cells were found mostly near the calcified areas. Strong osteocalcin immunostaining was seen in stromal cells and calcium deposits of CAVs. Increased numbers of RANKL and RANK positive cells were observed adjacent to calcified areas. OPG staining cells were absent near to areas of calcification. Conclusions: These data suggest that aortic calcification may be based on a chronic inflammatory process involving activated macrophages and T cell lymphocytes. Valvular fibroblasts probably differentiate into cells that possess characteristics of smooth muscle cells and may differentiate into osteoblast phenotype. Moreover, the expression pattern of the RANKL/RANK/OPG system suggests that it may have a regulatory role in the calcification process of human AVs.

An Endocardial to Epicardial Myocardial Contraction Gradient Is Present in Severe Compensated Aortic Stenosis: Does It Reverse after Aortic Valve Replacement?


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Introduction: Experimental animal aortic stenosis (AS) exhibits decreased subendocardial coronary flow and decreased subendocardial shortening. These abnormalities have been shown by us and others to rapidly normalize following relief of AS. In late, but compensated human AS, a subendocardial to subepicardial strain gradient (S_endo/S_epi) via CMR is present. Hypothesis: S_endo/S_epi myocardial strain gradient in severe AS reverses following aortic valve replacement (AVR) in concert with...
LVH regression. **Methods:** 32 patients with compensated AS underwent CMR RF tagging to assess intramyocardial strain (HARP, Palo Alto, Calif., USA) of the endocardial and epicardial shells for 8–12 short-axis slices pre, 6 and 12 months following AVR. **Results:** 18 of 24 patients had full 2D strain available. Following AVR, there was marked regression of LV mass (91 ± 39 vs. 77 ± 32 g/m²), LVEDVI and LVESVI (79 ± 25 vs. 69 ± 11 mL and 37 ± 29 vs. 23 ± 8 mL, respectively) while EF increased (58 ± 18 vs. 67 ± 10%) (p < 0.001 for all). For the group composed of CAD+ and CAD− patients, S\textsubscript{endo}/S\textsubscript{epi} strain was markedly abnormal pre AVR: 0.52 ± 0.33%, was 0.56 ± 0.51% at 6 months and 0.59 ± 0.49% by 12 months (all p = NS) remaining below historic controls (1.20 ± 40%). There was marked improvement in absolute strains when defined by endo, midwall and epi segments, over time (p < 0.05) and from base to mid (p < 0.05) excluding the apex. In pts with CAD and AS, the improvements in LV metrics post AVR were further blunted (p < 0.05). However, CAD− patients never achieved control absolute strain or S\textsubscript{endo}/S\textsubscript{epi} strain ratios. **Conclusion:** Subendocardial and subepicardium strains rapidly improve in parallel post-AVR but do not normalize, and remained more perturbed in those with CAD.

**Statins in Calcific Aortic Stenosis: A Meta-Analysis**  
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**Background:** Aortic stenosis (AS) is the most common cause of valve replacement in developed countries. Compelling data suggest that AS is an active disease process similar to atherosclerosis and that statins may be effective in delaying its progression. The objective of this meta-analysis is to determine the efficacy of statin treatment among patients with calcific AS. **Methods:** Clinical trials were identified with keywords: statins, aortic valve calcification, randomized controlled trials (RCTs). A total of 7 articles were queried, 2 of which are RCTs. They were subjected to data extraction, quality scale and included in the study. Included studies reported a total of 294 patients with mild to moderate calcific AS (Vmax 2.0–3.9 m/s); these were the subjects of our analysis. Patients were excluded if they also had more than mild aortic regurgitation, severe mitral valve stenosis, left ventricular dysfunction (ejection fraction <35%), planned aortic valve replacement, intolerance to statins, statin therapy or to potential benefit from statin therapy (according to the treating physician) and baseline serum cholesterol of less than 150 mg/dl, and presence of myocardial infarction. **Results:** of 294 patients with mild to moderate AS, 35% took statins that increased (58% vs. 67% of historic controls). **Conclusion:** Statins may be effective in delaying regression of obstruction during 2 years of treatment. Additional prospective, randomized trials, possibly with longer follow-up, will be necessary to more completely evaluate the use of these drugs in this setting.

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<th>Baseline characteristics</th>
<th>Treatment group (n = 198)</th>
<th>Placebo group (n = 199)</th>
<th>p value</th>
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**Valvular Heart Diseases in 82 Pathology Proven Cardiac Amyloidosis**  
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**Background:** Valvular involvement was reported in cardiac amyloidosis at autopsy and echocardiography. It is unknown how frequently valvular heart disease (VHD) is involved in different type cardiac amyloidosis and its clinical significance. **Methods:** 116 cardiac amyloidosis were identified at autopsy at Mayo Clinic. Echocardiograms were available in 82 cases with 44 primary (P) and 38 non primary (NP) type (33 senile, 3 secondary, 2 familial). We evaluated the severity and causes of VHD. Significant VHD was defined as at least moderate valvular regurgitation or stenosis in any valves. **Results:** The median time from echo to death was 30 days. Compared with NP, the P group was younger, had bigger RV/LV wall thickness and smaller LV diameter (all p < 0.05). However, the NP had a higher frequency of VHD than the P group (71 vs. 36%, p = 0.002). Furthermore, the NP had more severe VHD than the P group (30 vs. 9%, p = 0.02). The most common causes for VHD in P amyloidosis was thickened sclerotic valves causing leaflet immobility with poor coaptation and tricuspid annular dilatation (for tricuspid regurgitation (TR) only) (14/16) while mitral valve prolapse and thombosed tricuspid valve are the cause for regurgitation in 2/16 cases. Severe TR was detected in 4 P cases but no severe VHD in other valves in the group. In comparison, NP patients with severe VHD involved in mitral (7), aortic (1) as well as tricuspid valve (6) with prolapse (2), calcification (4), or annular dilatation (9) as the causes for the lesion. **Conclusions:** Although P amyloid patients have more advanced amyloid deposition, they had fewer significant VHD and fewer severe VHD than the NP patients. Severe VHD was only detected in the tricuspid valve in P amyloidosis while no severe lesion in other valves. Furthermore, the mechanism for severe VHD may be different in the P and the NP amyloidosis.
Two Institution Experience with 890 Video-Assisted Minimally Invasive Mitral Valve Surgeries

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Objective: Minimally invasive mitral valve (MV) surgery has become the standard of care at many institutions. We reviewed the experience of two centers using videoscopic assisted minimally invasive MV surgery (MIMVS). Methods: Retrospective chart review of all attempted MIMVS from 5/96 to 1/06. MIMVS was approached via right mini thoracotomy using videoscopic assistance and peripheral cannulation to establish CPB. Cardiac arrest was achieved using cold fibrillatory arrest or antegrade cardioplegia and transthoracic crossclamp (TTXC) or endoaortic balloon occlusion (EABO). Patient demographics, comorbidities, mortality, morbidities, and operative failures were recorded. Statistical analysis using Fisher’s exact and Pearson’s chi square tests were performed. Results: 890 patients underwent MV repairs (n = 706, 79%) or replacements (n = 184, 21%). Previous cardiac surgeries were performed in 129 (14.5%) patients. Mean age was 60.9 ± 14 years. Comorbidities included AFIB (n = 285, 32%), hypertension (n = 377, 42.4%), CAD (n = 134, 15.1%), and CHF (n = 553, 62%). Concomitant procedures occurred in 217 (24.4%) patients, including PFO closure (n = 43), left atrial appendage ligation (n = 146), pulmonary vein isolation (n = 109), CABG (n = 4), and TV repairs (n = 39). Thirty day mortality was 2.9% (n = 26). Complications included 14 strokes (1.5%), 14 conversions to sternotomy (1.5%), and 47 re-explorations for bleeding (5.2%). Six aortic dissections occurred, the higher incidence occurring in the EABO (n = 5) versus the TTXC group (n = 1) (p = 0.11). Length of hospital stay was 7.2 ± 6 days; blood transfusion rate of 36.4% and time to extubation averaged 16 ± 74 h. Twenty-five patients (2.8%) required MV reoperation. Conclusion: MIMVS alone or in combination with other cardiac procedures is safe and reproducible. EABO technique is associated with a higher but not significant incidence of aortic dissection. Long-term follow-up studies are necessary to ascertain the durability of MIMVS.

Clinical Profile of 21 Cases of ‘Mitral Valve Prolapse Syndrome’ from Rural India

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Data about the prevalence of mitral valve prolapse syndrome (MVP) are not available in rural India, where lack of availability of investigational facilities, poverty, and limited research funds preclude collection of such data. Clinical studies of MVP in the Indian pediatric population have been very few. Nonetheless, sub-population differences in rural versus urban India suggest that clinical sequelae of MVP also may differ in the regions. Therefore, we have collected clinical, radiological, electrocardiographic and 2D-echocardiographic findings in 21 patients with MVP who were seen at the Outpatient Department of Rajhans Hospital, a private hospital in the interior of Rural Maharashtra [Saphale], over a period of 5 years [December 1999 to December 2004]. Associations of MVP included Marfanoid features like–pectus excavatum, horizontal arm span > height, arachnodactyly, high arched palate, hypermobile joints and thin stall stature. The prevalence of MVP is relatively high compared with earlier reports in other populations (21/62,432 = MVPs/total patients examined over 5 years) and the distribution of symptoms also is unusual. Relatively isolated population, tradition of second/third degree consanguineous marriages and marriages within the community and/or caste [one of the hereditary social classes in Hinduism that restrict the occupation of their members and their association with the members of other castes] may account for the relatively high prevalence of MVP in this population. Also, genetic drift (gene frequency change caused by ‘finite’ population size) may explain the unusually high prevalence in this small, isolated population. Additional studies will be needed to properly define the basis for this clustering. The data from December 1999 to December 2004 was collected from record section of Rajhans Hospital by Dr. Sankalp Gokhale, who was working as Medical Officer in the Department of Pediatrics then from 5th March 2005 to 30th April 2005. The data was studied and analyzed retrospectively by Dr. S.G. Gokhale, Consultant, Department of Pediatrics and Neonatology, Rajhans Hospital and Pathology Laboratory.

Determinants of NYHA Class in Severe Organic Mitral Regurgitation. Results from the Mitral Regurgitation International Database (MIDA)

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Background: Determinants of NYHA Class in severe organic mitral regurgitation (MR) are poorly defined. A strong relationship between NYHA Class and the consequences of volume over-
load due to MR would support the currently recommended use of this parameter for patients’ follow-up and therapeutic decision making. **Methods:** We investigated 394 patients with MR due to flail leaflet who underwent trans- thoracic echocardiography and clinical evaluation at 4 European Tertiary Cardiology Centers from 1988 to 2004 (age 64 ± 11 years; 67% males; mean ejection fraction (LVEF) 67 ± 10%; 83% in sinus rhythm). All of the clinical and instrumental data were entered in the common MIDA database. **Results:** At the time of evaluation, 142 patients (36%) were in NYHA Class III–IV. Univariate predictors (p < 0.1) of NYHA Class III–IV were age, gender, diabetes, atrial fibrillation, coronary artery disease, renal insufficiency, heart rate, left atrial dimension, tricuspid regurgitation (TR) severity. At multivariate analysis, the following variables retained prognostic significance.

<table>
<thead>
<tr>
<th>OR (95% CI)</th>
<th>p value</th>
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<tr>
<td>Age, years</td>
<td>1.07 (1.04–1.09)</td>
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<tr>
<td>Renal disease</td>
<td>3.05 (1.04–9.01)</td>
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<tr>
<td>Left atrial diameter, mm</td>
<td>1.03 (1.00–1.06)</td>
</tr>
<tr>
<td>Moderate/severe TR</td>
<td>2.88 (1.58–5.23)</td>
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**Conclusions:** Although NYHA Class in MR is determined by the consequences of volume overload, a significant additional role appears to be played by non cardiac confounders (i.e. age and associated comorbidities). Therefore, the use of NYHA Class ‘per se’ as a follow-up tool or as an indicator for surgery can be questioned.

### Determinants of Recurrent Functional Mitral Regurgitation after Surgical Annuloplasty in Dilated Cardiomyopathy

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**Background:** Recurrence of mitral regurgitation (MR) after surgical mitral annuloplasty in patients with dilated cardiomyopathy and functional MR is not infrequent but poorly understood. We sought to identify echocardiographic determinants of recurrent MR in patients who underwent mitral annuloplasty in ACORN trial. **Method:** Of 184 Patients who underwent mitral valve surgery in ACORN trial (mean age 53.4 ± 12.6 years and mean left ventricular [LV] ejection fraction 27.5 ± 10.0%), 155 underwent mitral annuloplasty and 29 underwent mitral replacement. Eighteen (12%) patients with annuloplasty and 1 (3%) patient with replacement developed recurrent MR grade 2 or above at 6-month follow-up. Echocardiograms of patients with recurrent MR after annuloplasty (MR+ group) were compared with those of 34 patients (MR– group) with grade 1 or less MR after annuloplasty from the same trial. Anterior leaflet tethering angle (ATA), posterior leaflet tethering angle (PTA), tenting height (TH), LV end-diastolic (LVEDV) and end-systolic volume (LVESV), vena contracta (VC) and mitral annular area (MAA) were measured as shown in figure 1. **Results:** Preoperatively, MR+...
group had significantly greater ATA (29.4 ± 5.3 vs. 17.9 ± 4.4, p < 0.0001), TH (1.5 ± 0.4 vs. 1.0 ± 0.3 cm, p < 0.0001), LVEDV (367.3 ± 145.6 vs. 257.5 ± 81.7 ml, p = 0.002) and LVESV (291.3 ± 130.0 vs. 182.1 ± 68.0 ml, p < 0.0001) but similar VC, PTA and MAA. Preoperative ATA is the only independent predictor (p < 0.0001) of recurrent MR on multivariate analysis of all measured echocardiographic variables. Preoperative ATA > 26° accurately predicted recurrent MR and ATA < 20° accurately identified patients with no recurrence (fig. 2). Patients with ATA between 20° and 26° developed recurrent MR only when anterior leaflet tethering persisted after surgery (table 1). **Conclusion:** Patients with recurrent MR after mitral annuloplasty have more severe anterior leaflet tethering preoperatively. Measurement of preoperative ATA can accurately distinguish patients who will or will not develop recurrent MR. Relief of anterior leaflet tethering may prevent MR recurrence in a subset of patients.

**Restrictive Mitral Valve Annuloplasty for the Treatment of Ischemic Mitral Regurgitation: Do We Replace a Mitral Regurgitation by a Mitral Stenosis?**

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**Introduction:** Restrictive mitral valve annuloplasty (MVA) combined with coronary artery bypass graft (CABG) is the conventional approach for the surgical management of patients with ischemic mitral regurgitation (IMR). We hypothesized that the restriction of the mitral annulus could cause an obstruction to antegrade mitral flow that could, in turn, impact on patient’s functional capacity. **Methods and Results:** We performed a resting and dobutamine stress echocardiography (DSE) and a 6-minute walk test (6MWT) in 24 patients with IMR 1 year after restrictive MVA and CABG. In addition, 9 of these patients underwent stress exercise echocardiography. None of the 24 patients had more than 1+ mitral regurgitation after operation. At rest, peak and mean transmural gradients and mitral valve area were: 13 ± 4 mm Hg, 6 ± 2 mm Hg, and 1.48 ± 0.3 cm², respectively, which is similar to what is generally observed in patients with moderate to severe mitral stenosis. The average systolic pulmonary arterial pressure (SPAP) was 42 ± 13 mm Hg at rest, 63 ± 12 mm Hg during DSE and 69 ± 14 mm Hg during maximum exercise echocardiography. The 6MWT distance correlated with LV end-systolic diameter (r = 0.51, p = 0.015), peak mitral gradient (r = 0.78, p < 0.0001), and SPAP (r = 0.67, p = 0.001). On multivariate analysis, the peak gradient (Δr² = 0.59, p = 0.0003) and the SPAP (Δr² = 0.16, p = 0.004) were independently associated with shorter 6MWT distance. **Conclusion:** Our results show that the realization of restrictive MVA in patients with IMR may create a mitral stenosis. This hemodynamic sequel is associated with higher pulmonary arterial pressure and worse exercise capacity.
Novel NOTCH1 Mutations in Patients with Bicuspid Aortic Valve Disease and Thoracic Aortic Aneurysms
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Objectives: Bicuspid aortic valve (BAV) is a common condition, and one associated with a significantly increased risk of thoracic aortic aneurysms (TAA) and acute aortic dissection. Patient-specific prediction of the risk of TAA, however, is imprecise. We hypothesize that genotypic variations in BAV patients underlie this observed variability in aortic phenotype. We therefore investigated the potential relationship between mutations in regions of NOTCH1 recently reported to be associated with BAV, and the phenotype of BAV and TAA in unrelated patients undergoing surgical repair. Methods: We performed a targeted mutational analysis of NOTCH1 using genomic DNA from 48 unrelated subjects with concomitant BAV and TAA using denaturing high performance liquid chromatography (DHPLC) and direct DNA sequencing. We focused on exons in which mutations associated with BAV have been previously reported. Results were compared to control subjects with trileaflet aortic valves (TAV) (n = 94), BAV and normal aortas (n = 22), and subjects with TAV and TAA (n = 28). Results: Four unique, nonsynonymous (3 novel) variants were identified in 5 of 48 (10.4%) patients with concomitant BAV and TAA compared to only 3 of 144 (2.1%) control subjects (p = 0.02). Of these, two novel missense mutations, A1343V and P1390T, were observed only in patients with BAV and TAA. Conclusions: This targeted analysis involving NOTCH1 exons previously implicated in familial and sporadic BAV, demonstrates over-representation of NOTCH1 missense variants among patients with BAV and TAA. Identification of aneurysm-predisposing, susceptibility genes may lead to gene-directed surgical therapy of the ascending aorta for patients with bicuspid aortic valves.

Comprehensive Evaluation of Preoperative Patients with Aortic Valve Stenosis. Usefulness of Multi-Detector Cardiac Computed Tomography
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Background: Preoperative assessment of patients with aortic valve stenosis (AS) relies on the evaluation of AS severity (aortic valve area or AVA) and left ventricular ejection fraction (LVEF) by echocardiography, and of coronary artery anatomy by coronary angiography. We sought to evaluate the feasibility and accuracy of contrast-enhanced Multi-Detector-row Computed Tomography (MDCT), as a single non-invasive preoperative test, for simultaneous evaluation of the AVA, LVEF and coronary status in patients with AS. Methods: Forty consecutive patients with AS scheduled for aortic valve replacement underwent within one week a transthoracic echocardiography, a ECG-gated MDCT and a coronary angiography. Results: MDCT measurements could be performed in all patients. A good correlation but a slight overestimation was observed between AVA measured by MDCT and by echocardiography (0.87 ± 0.22 vs. 0.81 ± 0.20 cm², p = 0.01; r = 0.75, p < 0.0001). Mean difference between methods was 0.06 ± 0.15 cm². LVEF measured by MDCT correlated well with and did not differ from echocardiographic measurements (59 ± 13 vs. 61 ± 10%, p = 0.34; r = 0.76, p < 0.0001; mean difference 1 ± 8%). Coronary angiography displayed 33 lesions in 13 patients. MDCT correctly identified 26 of these 33 lesions and overestimated 3 less than 50% stenosis. On a segment-by-segment analysis, MDCT sensitivity, specificity, positive and negative predictive values were 79, 99, 90 and 98% respectively. Per patient, MDCT had a sensitivity of 85% (11/13 patients), a specificity of 93% (25/27 patients), and positive and negative predictive values of 85% (11/13 patients) and 93% (25/27 patients), respectively. Conclusion: MDCT can provide a simultaneous and accurate evaluation of the ABA, LVEF and coronary artery anatomy in patients with AS. In the near future, with technologic improvements, MDCT could achieve an exhaustive and comprehensive preoperative assessment of patients with AS. In addition, for the assessment of AS severity in difficult cases, MDCT could be considered as an alternative to transoesophageal echocardiography or cardiac catheterization.

Late Functional Results after Percutaneous Mitral Commissurotomy: Does Commissural Opening Matter?
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Background: Commissural opening is the main mechanism by which mitral valve area (MVA) increases after percutaneous mitral commissurotomy (PMC) but its specific prognostic impact on long term functional results has never been evaluated. Methods: We evaluated the outcome of 875 patients (48 ± 13 years, 83% female) with mitral stenosis (MS) and good immediate results of PMC (mitral valve area ≥ 1.5 cm² and no regurgitation >2/4). Good functional result was defined as survival without need for mitral surgery or repeat dilatation and NYHA functional class I or II at last follow-up. The 875 patients were divided into three groups: group 1 (n = 189) if both commissures were only partially opened or not split, group 2 (n = 459) if only one commissure was completely split and group 3 (n = 227) if both commissures were completely split. The prognostic impact of commissural opening was evaluated using a multivariate Cox model including 7 previously identified predictive factors of poor functional results: old age, high NYHA functional class, unfavorable mitral valve anatomy, atrial fibrillation, low post-procedure MVA, high post-procedure mean gradient, and grade 2 post-procedure mitral regurgitation. Results: Immediately after PMC, there were significant differences between the three groups as re-
Mitral Leaflet Separation Index: A New Method for the Evaluation of the Severity of Mitral Stenosis? Usefulness before and after Percutaneous Mitral Commissurotomy

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Background: Two-dimensional planimetry (MVA2D) is the reference method for the evaluation of the severity of mitral stenosis (MS) but requires experienced operators. The mitral leaflet separation (MLS) index (distance between mitral leaflets), has recently been presented as a reliable measure of MS severity. This method has the advantage of simplicity but has not been evaluated in a non-selected series of consecutive patients before and after percutaneous mitral commissurotomy (PMC).

Methods: Patients referred for MS evaluation in our institution between February and September 2006 were prospectively enrolled in the present study. The only exclusion criterion was non-feasible planimetry. MLS index was obtained by averaging the maximal leaflet separation distance at the tips in diastole in parasternal long-axis and apical 4-chamber views. Planimetry was used as reference.

Results: Ninety consecutive patients were enrolled and 116 examinations performed: 55 before PMC, 61 after PMC. Overall mean MVA2D was 1.48 ± 0.52 cm², MLS index 1.01 ± 0.24 cm and a good correlation between both measurements was observed (r = 0.77, p < 0.00001). MLS index was significantly different between patients with severe (MVA2D ≥1.5 cm²) and non-severe MS (0.87 ± 0.17 vs. 1.17 ± 0.21 cm, p < 0.0001) but there was an important overlap. No threshold value could predict a non-severe MS with both a sensitivity and a specificity >80%. A threshold value of 0.97 cm provided the best combination of sensitivity and specificity (86 and 75% respectively). However, an MLS index ≥1.2 cm provided a good specificity and positive predictive values (PPV) for the diagnosis of non-severe MS (85 and 89% respectively) and an MLS index <0.8 cm an excellent specificity and PPV for severe MS (98 and 96% respectively). Conclusion: MLS index cannot be considered as a substitute for MVA but can be used as a semi-quantitative and complementary method for the integrative assessment of MS severity.

Natural History of Patients with Asymptomatic, Normally Functioning or Minimally Dysfunctional Bicuspid Aortic Valve in the Community

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Background: Bicuspid aortic valve is a frequent congenital condition reported to cause numerous complications but the clinical outcome of patients diagnosed with yet normal or mildly dysfunctional valve is undefined. Methods: In 212 (32 ± 20 years, 65% male) consecutive asymptomatic community residents from Olmsted County, Minn., USA, bicuspid aortic valve was diagnosed between 1980 and 1999 with ejection fraction ≥50% and aortic regurgitation or stenosis absent or mild. Aortic valve degeneration was echocardiographically scored. Results: At diagnosis, ejection fraction was 63 ± 5% and left ventricular diameter 48 ± 9 mm. Survival 20 years after diagnosis was 90 ± 3%, identical to that of age-sex matched general population (p = 0.72) (Fig. 1). Twenty years after diagnosis heart failure, new cardiac symptoms and cardiovascular medical and surgical events occurred in 7 ± 2, 26 ± 4 and 33 ± 5%. Incidence of aortic valve surgery, ascending aortic surgery or any cardiovascular surgery at 20 years was 24 ± 4, 5 ± 2 and 27 ± 4% (Fig. 2A). Ascending aortic aneurysm occurred in 8 ± 3% at 20 years but no aortic dissection occurred. Thus, cardiovascular medical or surgical events occurred in 42 ± 5% 20 years after diagnosis (Fig. 2B). Independent predictors of cardiovascular events were age ≥50 (risk-ratio 3.0 [1.5–5.7], p < 0.01) and early valve degeneration (risk-ratio 2.4 [1.2–4.5], p = 0.016). Ascending aorta ≥40 mm at baseline independently predicted aortic valve degeneration (risk-ratio 9.8 [2.7–34.8], p < 0.01).

Conclusions: In the community, asymptomatic patients with bicuspid aortic valve and no or minimal hemodynamic abnormality, enjoy excellent long term survival but incur frequent cardiovascular events, particularly with progressive valve dysfunction. Echocardiographic early valve degeneration separates high-risk patients who require close monitoring from low-risk patients who require episodic follow-up.

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Valves in the Heart of the Big Apple V
Impact of Valvular Heart Diseases on Survival in the Community
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Background: Valvular heart diseases (VHD) are a significant public health problem. Overall survival in the community associated with specific valve diseases is unknown. Aim: To determine the impact on overall survival of specific left-sided valve disease in a geographically defined community. Methods: A cohort of adult Olmsted County, MN residents 18 years or older diagnosed with ≥ moderate MR, MS, AR, AS between 1990 and 1995 by clinically indicated echocardiography at the Mayo Clinic, Rochester, Minn., USA, were identified. Overall mortality of these community adults was determined up to the year 2004 and compared to age- and gender-matched expected survival for the community.

Results: 971 adult residents were included (55% female). Observed survival at 8 years was significantly less than expected for residents with MR (36 vs. 62%, p < 0.001), AR (51 vs. 67%, p < 0.001), AS (39 vs. 58%, p < 0.001), but not for MS (65 vs. 75%, p = 0.12). Females were more likely than males do die from VHD (male vs. female RR 0.74, 95% CI 0.62–0.88, p < 0.001). Risk of death from VHD was independent of LVEF, but was higher for LVEF > 50% compared to LVEF ≤ 50% (RR 2.2, 95% CI 1.86–2.63, p < 0.001). Aging increased the risk of death from VHD (RR per...
10 year 2.0, 95% CI 1.86–2.23, p < 0.001). Conclusion: In the community, overall survival associated with VHD is less than expected, regardless of the type of valve disease, except MS. Female gender and advancing age are associated with increased risk of death from VHD.

Prevalence of Bicuspid Aortic Valve in the Community
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Background: The prevalence of bicuspid aortic valve (BAV) in the general population is derived from autopsy studies or limited number of ante-mortem cases. Aim: The aim of this study was to determine the prevalence of bicuspid aortic valve in a large echocardiographic database of clinically indicated echocardiographic examinations in a geographically defined community. Method: Adult Olmsted County, MN residents 18 years and older who were alive at the time of the 2000 population census with previous echocardiograms were identified in the Mayo Clinic, Rochester echocardiographic laboratory database and included in the study if they had not previously declined participation in research. Results: 15,845 adult Olmsted County residents were included, age 58 ± 18, female 55%. A definite diagnosis of BAV was present in 217 residents or 1.4% and possible BAV in 56 residents or 0.4%. BAV was more common in men compared to women (67 vs. 33% for definite BAV and 70 vs. 30% for probable BAV). Conclusion: The prevalence of BAV in a large echocardiographic database of clinically indicated echocardiograms in the community is 1–2%. BAV is more common in men than women.

Unusual Sequential Pulmonary Outflow Obstruction in an Adult with Corrected Tetralogy of Fallot
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Introduction: Obstruction to the pulmonary outflow is relatively rare in adults. In this report we describe a case of unusual and serial obstruction to right ventricular blood flow in an adult with history of corrected tetralogy of Fallot. Case Report: A 49-year-old female came to our attention with complaints of progressive dyspnea. Significant past history included multiple surgeries for Tetralogy of Fallot. She had a classic Blalock Taussig shunt in infancy followed by correction at 3 years of age with closure of ventricular septal defect and placement of a valve in the pulmonary position. There was a revision of right ventricular outflow tract (RVOT) at age of 15 with replacement of the pulmonary valve. Other significant medical history included hypertension, previous stroke and cocaine abuse presenting with shortness of breath and decreased exercise tolerance. Physical exam was significant for a 4/6 ejection systolic murmur in pulmonary area. EKG showed normal sinus rhythm with right atrial enlargement and complete RBBB. Echocardiogram showed moderate pulmonary outflow stenosis with mean pulmonic gradient of 31 mm Hg. There was no evidence of any residual VSD. Transesophageal echocardiogram revealed a prominent pyramidal fibromuscular ridge measuring 1.5 × 0.9 cm encroaching into the RVOT and immediately below the pulmonary valve. The diameter of the RVOT measured 1 cm with a peak systolic gradient of 50 mm Hg. Right heart catherization confirmed the gradient of 32 mm Hg across the RVOT. Pulmonary angiography revealed additional significant stenosis of the proximal left pulmonary artery. The right pulmonary artery was significantly dilated – thereby raising a suspicion of TOF with absent pulmonary valve as the initial diagnosis. The RVOT was successfully dilated and a stent was placed across the RVOT and pulmonary valve with no residual gradient. In addition balloon angioplasty was also performed for the stenotic left pulmonary artery. Discussion: Pulmonary outflow stenosis is a relatively rare heart condition encountered in adults. The optimal treatment strategy depends mainly on presence of symptoms and degree of transpulmonic valvular gradient. Our case is interesting because it represents a rare multi-level obstruction to the RV blood flow. Our patient had a subpulmonic ridge and left pulmonary artery significant stenosis. This was successfully treated with ballooning of the left pulmonary artery and stent placement across the infundibular stenosis.

Cleft Mitral Valve in Adults: The Role of 3D Echo in Diagnosis and Surgical Planning
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Introduction: Cleft mitral valve is a rare congenital anomaly, usually associated with other cardiac malformations such as endocardial cushion defects (ESD), secundum type atrial septal defect (ASD), ventricular septal defect (VSD) or transposition of the great arteries. The cleft usually involves the anterior leaflet and clinical manifestations include mitral insufficiency, subaortic outflow obstruction or both. We report the potential advantage of live three-dimensional transthoracic echocardiography (3DTTE) in the diagnosis and assessment of cleft mitral valve morphology and accessory chordae in a patient studied by us. Case: A 35-year-old male who presented with shortness of breath for three months. No significant prior medical history. Physical examination was significant for holosystolic murmur best heard at the apex and at the left sternal border. Electrocardiography showed left ventricular hypertrophy. The two-dimensional transthoracic echocardiogram (TTE) showed moderate concentric hypertrophy, normal LV function, moderate mitral regurgitation and prolapsed anterior mitral leaflet. In addition, a cleft in the anterior mitral leaflet was suspected and a sub-aortic, perimembranous ventricular septal defect was noted on TTE. The patient had 3DTTE, was confirmed cleft mitral leaflet with accessory chordal attachments noted within left ventricular outflow tract. The patient was managed medically and referred to cardiothoracic surgery for further evaluation for mitral valve replacement and VSD closure. Discussion: In contrast to two-dimensional echocardiography, the 3DTTE imaging has a number of advantages, it provides a de-
Papillary Muscle Rupture: A New Therapeutic Paradigm for an Old Disease?

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**Background:** Acute mitral regurgitation (MR) caused by papillary muscle rupture (PMR) is an infrequent but catastrophic complication of myocardial infarction (MI). Although always considered, surgical treatment is often denied or delayed because of the high operative mortality. Furthermore, the effects of surgery for PMR on the long-term outcome are largely undefined.

**Methods:** 54 consecutive patients (aged 70 ± 8 years, 74% male) who underwent mitral valve (MV) surgery for PMR from 1980 through 2000 were analyzed. **Results:** 52 patients (96%) presented with pulmonary edema and/or cardiogenic shock at the time of surgery, despite a left ventricular systolic function only mildly decreased (ejection fraction 55 ± 13%). Operative mortality (i.e., death within 30 days from the operation) was overall 18.5%. The only predictor of operative mortality was the association of coronary artery bypass to MV surgery OR [95%CI]: 0.18 [0.04–0.83], p = 0.028. During a mean follow-up of 6.4 ± 4.9 years, 59 deaths were recorded. At 5 years survival was 65 ± 6%, overall. When patients who died within 1 month after surgery were excluded from the analysis (n = 10), 5 years survival turned out to be 80 ± 6%, with a survival free from heart failure (HF) of 73 ± 7%. No predictors of long term outcome were identified. **Conclusions:** This study indicates that despite a high operative mortality, surgery for PMR provides favorable effects on long term outcome, and therefore should not be denied in the early post MI phase. Furthermore, once survived the operation, long term survival and survival free from HF turned out to be in this group of patients relatively favorable.

Optimal Treatment of Combined Aortic Valve Disease and Ascending Aortic Aneurysm with Freestyle Aortic Root Replacement and Prosthetic Graft Replacement of Ascending Aorta

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**Background:** For patients presenting with concomitant aortic valve disease and aneurysm of the ascending aorta (AA), third-generation stentless bioprostheses combined with prosthetic grafts allow for removal of all diseased aortic tissue. **Methods:** Ten patients underwent concomitant aortic root replacement with Medtronic Freestyle aortic root bioprosthesis and replacement of the AA with a prosthetic graft. Mean patient age was 63 (range 28 to 81). Presenting diagnosis was aortic stenosis in 5 patients, aortic insufficiency in 2 patients, combined stenosis/insufficiency in 1 patient, and other in 2 patients. All patients had aneurysms of the AA. Concomitant operations included coronary artery bypass grafting in 3 patients, mitral valve repair in 1 patient, tricuspid valve repair in 1 patient, and radiofrequency Maze III operation in 2 patients. Two patients had reoperations. **Results:** There were no intraoperative mortalities or complications. Mean crossclamp time was 143 min (range 97–209) and mean cardiopulmonary bypass time was 195 min (range 142–259). For three patients requiring hemiarch reconstruction, mean circulatory arrest time was 15 min (range 13–16). Median size of Freestyle root was 29 mm and median size of the prosthetic graft was 30 mm. All patients were discharged in good condition and were well at last follow-up. **Conclusions:** Combined aortic root replacement with Freestyle aortic bioprosthesis and replacement of the ascending aorta with prosthetic graft is a safe and effective operation for the treatment of concomitant aortic valve disease and AA aneurysm.

Surgical Treatment of Functional Ischemic Mitral Regurgitation: A Long-Term Outcome Study

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**Background:** Functional ischemic mitral regurgitation (IMR) is the regurgitation due to the left ventricular consequences of ischemic heart disease despite a structurally normal valve. Recent data suggest that IMR contributes to high cardiac morbidity and mortality. However, surgical treatment of IMR is often denied because it is considered high risk and because long-term results are considered unfavorable. Nevertheless, outcomes following surgery in the most recent period are poorly known and may challenge this old paradigm. **Methods:** The clinical outcome of 385 consecutive patients (aged 69 ± 9 years, 56% male) who underwent surgery for IMR from 1980 to 2000 were analyzed. **Results:** Valve repair (MRep) (n = 267) and replacement (MVR) (n = 118) were performed in patients with similar baseline characteristics in terms of age, male prevalence and EF (p ≥ 0.12), but prevalence of NYHA class III–IV was higher in MVR patients (83 vs. 66%, p < 0.001). Operative mortality was overall 12.5% (9.4 MRep vs. 19.5% MVR, p = 0.007) and decreased from 21 ± 3% before 1990 (n = 152) to 6.9 ± 2% after 1990 (n = 233), p < 0.001. During a mean follow up of 5.4 ± 4.7 years, 272 deaths were recorded. In multivariate analysis MRep was an independent (from age, EF, creatinine) predictor of better long-term survival (adjusted HR [95%CI]: 0.66 [0.49–0.88], p = 0.006). At 5 years, overall survival was 47 ± 2%, 58 ± 3% in MRep and 43 ± 4% in MVR, p = 0.011. The benefits of MRep over MVR were more prominent in patients with EF above 40%. **Conclusions:** This study confirms the high risk associated with IMR, especially with...
low EF. Operative mortality remains notable although it has significantly decreased during the last decade. MRep appeared beneficial over MVR, particularly in patients with only mild left ventricular dysfunction. These recent improvements are encouraging in offering surgical treatment of IMR before intractable complications occur.

**Improved Results of Tricuspid Valve Repair Using Undersized Annuloplasty Rings**

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**Objective:** Starting in July 2000 we have exclusively used 26 and 28 mm tricuspid annuloplasty rings independent of the size of the annulus. This study was undertaken to evaluate the efficacy of tricuspid valve annuloplasty using undersized rings as compared to conventionally sized rings. **Methods:** Between 1987 and June 2006, 98 patients have had tricuspid valve repair concomitant with other cardiac procedures at our institution by one surgeon (SH). In the year 2000 we started using undersized annuloplasty rings in the tricuspid position with the hypothesis that this would provide for a more durable repair. We have used 26-mm Carpentier-Edward rings for patients with BMI less than 1.7 m², and 28-mm rings if the BMI exceeds 1.7 m². **Results:** The mean age of the patients was 70.7 years. Ninety percent (n = 88) had a concomitant mitral valve procedure. There was no in-hospital mortality. The average echocardiographic follow-up was 4.8 years. Twenty-five percent (n = 8) of the patients treated prior to the year 2000 and 11% (n = 7) of those treated after the year 2000 developed moderate tricuspid regurgitation (p = 0.03). There were no instances of clinical or echocardiographic tricuspid stenosis. Use of a permanent pacemaker was necessary in 15.6% (n = 5) and 12.1% (n = 8) of the patients in the two time periods respectively. There were no reoperations for severe TR. **Conclusion:** Significant reduction of the tricuspid annulus using small ring sizes resulted in marked decrease of recurrent tricuspid regurgitation. In our series this technique resulted in more than 50% decrease in the incidence of significant recurrent tricuspid regurgitation.

**Cardiac Resynchronization Therapy and Mitral Regurgitation**

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**Background and Methods:** Cardiac resynchronization therapy (CRT) is beneficial in patients with heart failure and has been shown to reduce mitral regurgitation (MR). However, the mechanism of MR reduction is unclear. We aimed to examine the effect of CRT on mitral valve geometry. 12 patients underwent 3D and 2D echocardiography pre-CRT (within 24 h of implant) and at 3 months post-CRT. Dyssynchrony (max delay between segments (MTD), MR (vena contracta = VC), LV volumes (end-diastolic = EDV; end-systolic = ESV) and sphericity index (EDV or ESV/ 4/3 (II) (r²); r is length of LV) were measured. Mitral valve annular area (MAA), annular shape (medial-lateral, anterior-posterior dimensions) and tenting volume (TV: volume from leaflets to annular plane) were measured using 3D echo. **Results:** Dyssynchrony improved post-CRT (MTD 108 ± 31 to 86 ± 32, p = 0.004). VC decreased (3.8 ± 3.5 to 2.4 ± 2.7 mm, p = 0.13). LV volumes (EDV: 241 ± 119 vs.199 ± 89 ml, p = 005; ESV: 187 ± 98 vs. 125 ± 49 ml, p < 0.001) and sphericity index (ED: 0.48 ± 0.1 vs. 0.43 ± 0.8, p = 0.03; ES: 0.52 ± 0.09 vs. 0.43 ± 0.06) decreased, consistent with a less spherical LV post-CRT. EF increased (24 ± 6 vs. 28 ± 8%, p = 0.02) post-CRT. MAA (11.4 ± 3.9 to 10.3 ± 4.2 cm², p = 0.008, figure 1) and TV (4.4 ± 2.1 to 3.3 ± 1.5 ml, p = 0.02) decreased significantly post-CRT. Both medial-lateral and anterior-posterior annular dimensions decreased significantly post-CRT (ML: 39 ± 6 vs 35 ± 7, p = 0.04. AP: 36 ± 7 vs 33 ± 7, p = 0.04). **Conclusions:** CRT results in a decrease in LV volumes and a less spherical LV shape. This is accompanied by decreased mitral annular area and mitral leaflet tenting volume.
Risk of Recurrent Gastrointestinal Bleeding after Aortic Valve Replacement in Patients with Heyde Syndrome

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Objective: Heyde syndrome refers to the association of gastrointestinal (GI) bleeding from arteriovenous malformations (AVMs) and aortic valve stenosis. Von Willebrand factor abnormalities are directly related to the severity of aortic stenosis, and may be improved by valve replacement. The objective of this project is to determine the effectiveness of aortic valve replacement (AVR) in reducing GI bleeding in patients with Heyde syndrome.

Methods: From 1971 through 2003, 57 patients with AVMs and GI bleeding underwent AVR. We analyzed early and late outcomes, including recurrent GI hemorrhage, defined as bleeding from an AVM or unknown source. Results: At operation, the median age of the 39 men and 18 women was 75 years (range 33 to 93 years). Bleeding AVMs were identified predominantly in the duodenum and right side of the colon (duodenum 26%, right colon 30%, both duodenum and right colon 12%, and other 32%). Prior to AVR, the mean number of bleeding episodes was 12 per patient-year (range 1 to 116); 48 patients (84%) required blood transfusions (median 7 units, range 1 to 40 units/pt). Bioprosthetic valves were used in 47 patients, and mechanical valves were implanted into the remaining 10. Perioperative mortality was 3.5%, and 5 and 10 year survivals were 65 and 47%. During follow-up extending to 15 years (median 4.4 years), 41 patients (72%) had no further bleeding and appeared cured. Fourteen patients experienced recurrent GI bleed, but the frequency of bleeding events was reduced to 2.8 per patient-year. The 10 year cumulative probability of bleeding was 28% (95% CI 12–42%). Rebleeding occurred only in patients with lesions in the duodenum or right colon and there was a significant difference in the rate of rebleeding between those with concomitant duodenal and right colon lesions versus patients with AVMs in only one of those locations (rebleed rates: concomitant 71%, duodenum 19%, rt colon 35%, p < 0.05). Among patients who received bioprostheses, overall risk of rebleeding was 20%; this was lower than the 50% risk of subsequent gastrointestinal bleeding in patients with mechanical prostheses (p = 0.69). Conclusions: AVR appears to decrease the risk of GI bleed in patients with Heyde syndrome and is curative in 72%. Rebleeding was only seen when the AVM was located in either the duodenum or right colon. Although rates of rebleeding were not significantly different between the two prosthetic valve types, the higher risk of bleeding in patients receiving Coumadin makes bioprostheses the valve of choice for most patients.

Long-Term Quality of Life in Nonagenarians following Valve and Non-Valve Cardiac Surgery


Objective: To explore long-term quality of life among a cohort of surviving nonagenarians who underwent cardiac surgery.

Methods: A series of 49 patients underwent surgery between 1995 and 2004; 23 survivors were identified in 2005. Of these survivors, 12 patients were excluded (neurocognitive decline, n = 7; refusal, n = 4; non-English speaking, n = 1). Eleven (48% of survivors) patients completed the interview. Of these, six were valve patients (i.e. valve-only, concomitant CABG/valve) and five non-valve (i.e. CABG only, thoracic aortic procedure, concomitant CABG/thoracic aortic procedure). Baseline characteristics and survival outcomes were retrospectively reviewed. In 2005, patients were re-
contacted and quality of life was assessed using the SF-12 Health Survey. **Results:** The mean age at the time of surgery was 91.8 ± 0.2 years and 81% were male. At follow-up, a mean of 3.7 ± 2.2 years had elapsed since surgery. Valve surgery patients scored lower than non-valve patients in the physical, social, role-emotional, mental health, energy, bodily pain and role-physical domains of the SF-12, but the differences were not significant (fig. 1). Both valve and non-valve patients reported better function in all domains of the SF-12 when compared to normative data for cardiovascular disease patients aged 75 years or greater. Overall survival was 5.7 ± 2.3 years for valve patients and 7.3 ± 2.1 years for non-valve patients. **Conclusion:** Quality of life and survival is favorable among this small sample of long-term nonagenarian cardiac surgery survivors relative to normative cardiovascular data. There are no significant differences in quality of life or survival outcomes between valve and non-valve survivors.

**Outcomes Analysis between Valve and Non-Valve Cardiac Surgery in Nonagenarians**


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**Background:** Early research on cardiac surgery in nonagenarians has demonstrated that surgical intervention is a viable therapeutic option in these patients. Intricacies of such intervention relative to valve and non-valve procedures have yet to be explored. **Methods:** A consecutive series of 49 nonagenarians who underwent valve surgery (i.e. valve-only, concomitant CABG/valve) or non-valve surgery (i.e. CABG only, thoracic aortic procedure, concomitant CABG/thoracic aortic procedure) between 1995 and 2004 were retrospectively reviewed. **Results:** Age and gender of the overall cohort was similar; mean age was 91.9 ± 1.6 years and 51% were male. Baseline comorbidity for the valve and non-valve groups included hypertension (88 vs. 67%), diabetes (20 vs. 8%) and stroke (20 vs. 8%) (p = ns for all). Valve patients were significantly more likely to have a history of CHF (p = 0.01), whereas non-valve patients more often had history of prior MI (p = 0.003). Fewer valve patients required emergent surgical intervention (17 vs. 48%, p = 0.02). Perioperatively, valve patients had significantly longer bypass and cross clamps times (p = 0.02). Postoperatively, valve patients experienced longer total hospital LOS (mean, 24 ± 23 vs. 16 ± 25 days; p = ns). Thirty-day mortality was 4% in valve patients and 8% in non-valve patients. Postoperative complications such as stroke (17 vs. 8%) and respiratory failure (33 vs. 12%) were higher in the valve group, but the difference was not significant. Long-term survival was similar between the groups as valve patients survived 3.6 ± 2.2 years and non-valve patients survived 3.4 ± 2.9 years. **Conclusion:** Valve surgery in nonagenarians is associated with longer operative time, less surgical urgency, longer LOS, and similar long-term survival when compared to non-valve patients.