		Relative MEK Activity (AR-CF:NL-CF)	
Cell Pair	**AR-RF(%)**	**MEK-4**	**MEK-7**
AR1 vs NL1	14	1.4:1	1.4:1
AR2 vs NL2	25	1.4:1	1.4:1
AR3 vs NL3	45	1.9:1	1.5:1
AR4 vs NL4	54	2.5:1	2.2:1
AR5 vs NL5	72	2.1:1	2.2:1

1067-136 Beta-Adrenergic Receptor Kinase Is Overexpressed in Patients With Chronic Mitral Regurgitation

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Background: Mitral regurgitation (MR) imposes a volume overload on the left ventricle (LV) during which LV ejection fraction remains normal, while LV contractility deteriorates. We have reported that LV contractile dysfunction is directly related to a decrease in responsivity of the β-adrenergic receptor (β-AR_1), but the mechanism for this reduced responsivity in *chronic* MR patients has not been explored. We hypothesized that this decrease in β-AR_1 responsivity may occur because of increased β-adrenergic receptor kinase (β-ARK_1) expression. **Methods**: Endomyocardial biopsy samples were obtained from four normal donor hearts and eight patients with *chronic* MR. Standard Affymetrix® chip technology was employed to analyze the samples for expression of β-ARK_1, β-ARK_2, β-AR_1, β-AR_2, and β-AR_3. The expression data were optimized to the standard, probe-pairs were quantile normalized, and the data were expressed as a fold-change for the MR patients compared to the normal donor hearts. Then, simplified t-tests were applied to the log transformed data. **Results**: Seven of the eight MR patients had LV contractile dysfunction but normal LV ejection fractions. Compared to the normal donor heart data, β-ARK_1 expression was 1.82 fold greater (p = 0.03), while β-ARK_2 and ß-arrestin expression were unchanged (1.00 and 0.94 fold change, p=0.27 and 0.31, respectively). The β-AR expression was not different between the two groups with β-AR_1 changing 0.56 fold (p=0.11), β-AR_2 changing 0.93 fold (p=0.72); and β-AR_3 changing 1.05 fold (p=0.79). **Conclusion**: β-ARK_1 expression is elevated in chronic MR patients with LV contractile dysfunction but normal LV ejection fractions, while β-AR expression is relatively unchanged. These data support the hypothesis that the decrease in β-AR_1 responsivity in these *chronic* MR patients may, in large part, be due to modification of β-AR_1 functionality through β-ARK_1 overexpression.

1067-137 Long-Term Afterload Reduction Halts Progression of Left Ventricular Dysfunction in Patients With Chronic Compensated Severe Mitral Regurgitation

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Background: Although afterload reduction is known to have favorable acute hemodynamic effects in patients with mitral regurgitation (MR), limited data exist concerning long-term effects. Our study examined whether afterload reduction slows progression of left ventricular (LV) dysfunction in stable asymptomatic patients with severe chronic MR.
Methods: A retrospective cohort study was conducted in patients with moderate-severe MR (3-4+) and an LV ejection fraction (EF) of ≥ 0.5, both determined by Doppler-echocardiographic visual estimate. The EF at 2 points in time from 48 patients not receiving afterload reduction during the interval (Group 1) and 45 patients receiving continuous afterload reduction both prior to and continuously during the observation period (Group 2) were compared.
Results: Groups 1 and 2 differed in age (69±17 years vs. 77±10, respectively, p=0.01) and EF (below, p=0.02), but not by gender, etiology of MR, symptoms, proportion treated with digoxin and beta blockade, chamber dimensions, severity of MR, blood pressure and heart rate. The average interval between examinations was 17±12 months (Group 1) and 20±14 (Group 2) p=0.2. Afterload reduction included ACE inhibitors (78%), calcium blockers (42%), angiotensin receptor blockers (20%), and vasodilators (4%). In Group 1, EF decreased from 62.0±7.5% to 59.7±6.7% (p=0.02) while Group 2 increased from 58.7±5.8% to 59.4±7.6%, (p=0.84). The changes observed in Group 1 (-2.3% over 17 months) was significantly different from Group 2 (+0.7 over 20 months) p=0.05. LV dimensions, MR severity, blood pressure and heart rate did not change.
Conclusions: In hemodynamically stable asymptomatic patients with severe chronic MR, long-term afterload reduction may halt progression of LV dysfunction.

1067-138 Dynamic Changes of the Tricuspid Annulus and Papillary Muscles During the Cardiac Cycle

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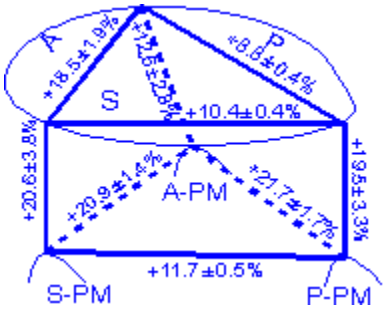
BACKGROUND: Knowledge of the normal dynamics of the cardiac valves is essential for understanding their pathologic changes and the design of surgical solutions. Although these geometric changes have been extensively studied in the aortic and mitral valves, the tricuspid valve has been largely ignored.
METHODS: Ten sonometric crystals were implanted in 7 sheep at midpoints of base of septal (S), anterior (A), and posterior (P) leaflets, tips of papillary muscles (PM), and apex.
RESULTS: Annulus area expanded from min 4.8± 0.3 cm^2 to max 6.1± 0.3 cm^2 (+28.6± 1.4%). Annulus perimeter expanded by 10.5± 0.5% (S), 13.0± 0.6% (A), and 14.0± 0.6% (P) leaflets. Increase in distance between commissures, PM, and commissures to PM are shown. The area from S-PM, A-PM, and P-PM expanded from 2.7± 0.2 cm^2 to 3.6± 0.2 cm^2 (+37.3± 3.8%). Angles between the annulus least squares plane and PM to the corresponding commissure axis changed at S-PM from 80.4± 3.3° to 94.3± 3.6° ; at A-PM from 67.8± 3.2° to 92.6± 3.4° , and at P-PM from 81.0± 2.3° to 90.4± 2.4° .
CONCLUSIONS: 1) the annulus' septal portion changes significantly during the cardiac cycle, and 2) at max displacement, all 3 PM were within the perimeter of the annulus. These findings should generate new tricuspid valve repair techniques.



1067-139 Is Visual Assessment a Valid Tool to Assess the Severity of the Mitral Regurgitation in Clinical Trials?

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Background: Although several semi-quantitative methods (SQM) for assessing the severity of mitral regurgitation (MR) have been validated, visual assessment (VA) of MR continues to be the easiest and the most popular means in clinical practice and clinical trials. This study aimed to validate VA by comparing it with the SQM in clinical trial that requires the assessment of MR. Methods: From the baseline data of Acorn cardiac support device trial, 111 cases with dilated cardiomyopathy and functional MR were identified. In these patients, the severity of MR was assessed by VA and compared with SQM including effective regurgitant orifice area (EROA), regurgitant volume (RV), MR area (MRA) by color Doppler test, MR area/left atrial area (MR/LA), MR distance (MRD), and vena contracta (VC). Results: The severity of MR by VA was grade I in 29, II in 22, III in 29, IV in 31 patients. The severity of MR by VA showed significant correlation with those by EROA (r = 0.75, p = 0.0006), RV (r = 0.76, p = 0.0004), MRA (r = 0.87, p < 0.0001), MR/LA (r = 0.91, p < 0.0001), MRD (r = 0.89, p < 0.0001), and VC (r = 0.88, p < 0.0001). With the increase of the MR severity by VA, the absolute values measured by SQM increased significantly.

	Grade I	Grade II	Grade III	Grade IV	p value
EROA (cm^2)	0.08±0.05	0.16±0.05	0.28±0.04	0.32±0.05	0.0150
RV (ml)	10±5.2	23±4.5	37±3.6	39±4.5	0.0024
MRA (cm^2)	3.7±0.6	6.3±0.6	9.1±0.6	14.8±0.5	< 0.0001
MR/LA (%)	15±2	26±2	37±2	53±2	< 0.0001
VC (mm)	2.0±0.3	2.5±0.2	3.6±0.2	5.8±0.2	< 0.0001

Conclusion: Visual assessment of the MR severity in patients with functional MR was consistent with those by various semi-quantitative methods. The semi-quantitative measures may serve as useful tools to assess the natural history of functional MR and the impact of medical and surgical interventions.

1067-140 Subnormal Tissue Inhibitor of Metalloproteinase Expression Modulates Matrix Metalloproteinase-2 Activity and Fibrosis in Aortic Regurgitation

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Background: Chronic aortic regurgitation (AR) is a predictable cause of heart failure. In our AR rabbit model, marked fibrosis is associated with hyperexpression of glycoproteins but not myocardial collagen content. We have shown that matrix metalloproteinase-2 (MMP-2), involved in collagen remodeling, is upregulated in AR and may suppress collagen content. MMP-2 activity can be modulated by endogenous tissue inhibitor metalloproteinases (TIMPs). To assess the role of TIMPs in regulating MMP-2 activity in AR, we assayed TIMP-1 and –2 expression by RT-PCR. Methods: Cardiac fibroblasts (CF) were cultured from NZW Rabbits without (NL)[n=3] and with surgically induced AR [n=3]. Total RNA was isolated [passage 6] from CF grown in triplicate. First-strand cDNA was synthesized from RNA using reverse transcriptase (RT) and was amplified by PCR using TIMP-1, TIMP-2 and GAPDH primers. The resulting products were resolved on ethidium bromide-stained agarose gels and scanned; band intensities were calculated using Kodak Digital Imaging and software. The TIMP band intensities for each sample were normalized to GAPDH and expressed as a ratio. Results: Quantitative analysis of TIMP-1[p=0.01] and TIMP-2 [p=0.06] gene expression show downregulation in AR-CF vs. NL-