Mitral Valve Disease in Circulation and the Circulation Subspecialty Journals

The Editors

The following articles are being highlighted as part of Circulation’s Topic Review series. This series will summarize the most important manuscripts, as selected by the editors, published in Circulation and the Circulation subspecialty journals. The studies included in this article represent the articles related to mitral valve disease that were published in Circulation and the Circulation subspecialty journals in 2010 and 2011. (Circulation. 2012;125:e529-e537.)

Features of Carcinoid Heart Disease Identified by 2- and 3-Dimensional Echocardiography and Cardiac MRI

Summary: Carcinoid heart disease is a common complication and a major cause of morbidity in patients with carcinoid syndrome. The classic echocardiographic features of tricuspid and pulmonary valvular dysfunction are well recognized. The role of newer imaging modalities including 3D echocardiography and cardiac MRI has been not been established. The current study prospectively assessed a large cohort of patients with carcinoid syndrome for features of carcinoid heart disease using a variety of imaging modalities, including both 2D and 3D transthoracic and transesophageal echocardiography as well as cardiac MRI. A spectrum of disease from early to advanced disease was identified. The extent and severity to which each valve leaflet or cusp and its associated subvalvular apparatus was affected was highly variable, producing a wide range of appearances. Three-dimensional transthoracic and transesophageal echocardiography are particularly useful in identifying pathology in the pulmonary and tricuspid valve, as all leaflets may not be visualized on 2D echocardiography. Cardiac MRI allowed quantification of the size of cardiac metastases and the extent of their invasion into the myocardium. Positron emission tomography imaging allowed functional assessment of metastases. The study recommends an integrated approach using multiple modalities in patients at risk of carcinoid heart disease to identify pathology and assess severity of disease.

Conclusions: Carcinoid heart disease is a heterogeneous disease with a wide spectrum of echocardiographic findings. A multimodality approach is needed in patients with this complex pathology.

Mitral Annular Dynamics in Myxomatous Valve Disease: New Insights With Real-Time 3-Dimensional Echocardiography

Summary: The mitral valve is formed by leaflets (1 anterior and 1 posterior) attached to the ventricular wall (by chordae and papillary muscles) and by the annulus, a fibrous ring-shaped structure that attaches leaflets to the base of the heart. The mitral annulus has been little studied because of the difficulty in imaging this wide structure completely and quickly enough. Real-time 3-dimensional echocardiography is a new technology that allows imaging of a pyramid of the heart structure at high speed. We used this new technology to image the mitral annulus, to define its characteristics and dynamics in patients with myxomatous valve disease in contrast to normal control subject, and to assess ischemic mitral regurgitation. First, we validated annular measurements by real-time 3-dimensional echocardiography versus direct intraoperative dimension. Second, we found that the normal mitral annulus is dynamic with complex changes throughout the cardiac cycle. Early during systole, normal annulus shows contraction with shape changes similar to a mouth with lips pursed, bringing leaflets closer and allowing the valve to remain competent while it is not yet “locked.” Later during systole, the annulus returns to its baseline size without excess enlargement. The myxomatous valve disease annulus is dynamic but different, losing regurgitation-preventive mechanisms, with ventricular-annular contraction decoupling and later excess enlargement contributing to leaflet separation. The wide and dynamic myxomatous valve disease annulus also contrasts with the narrow and mostly adynamic ischemic mitral regurgitation annulus. These new insights by real-time 3-dimensional echocardiography provide a new understanding of the mitral pathophysiology and should lead to improved repairs and annuloplasty, percutaneous or surgical, to improve long-term outcomes.

Conclusions: Real-time 3-dimensional transesophageal echocardiography provides insights into normal, dynamic mitral annulus function with early-systolic area contraction and saddle-shape deepening contributing to mitral competency. Myxomatous valve disease annulus is also dynamic but considerably different with loss of early-systolic area contraction and saddle-shape deepening despite similar magnitude of ventricular contraction, suggestive of ventricular-annular decoupling. Subsequent area enlargement may contribute to mitral incompetence. After mitral repair, myxomatous valve disease annulus remains dynamic without systolic saddle-shape accentuation. Thus, real-time 3-dimensional transesophageal echocardiography provides new insights that allow the refining of mitral pathophysiology concepts and repair strategies.

Direct Transthoracic Access to the Left Ventricle for Catheter Ablation of Ventricular Tachycardia

Summary: Radiofrequency ablation is a recognized therapy for ventricular tachycardia, but it depends on access to either the endocardium or epicardium. However, in patients with combined mitral and aortic valve replacement, either approach may not be feasible. This report describes a novel approach in such patients with direct transthoracic access. Two methodologies are described: The first is a direct percutaneous puncture, and the second uses a minithoracotomy.

Conclusions: Direct percutaneous left ventricular puncture is a viable option for mapping and ablation of left ventricular tachycardia. A
minithoracotomy allows better hemostatic control. This technique has a role when other percutaneous approaches are contraindicated.\(^3\)

**Early Surgery Versus Conventional Treatment in Asymptomatic Very Severe Aortic Stenosis**

**Summary:** Management of asymptomatic patients with very severe aortic stenosis remains controversial, and the combined risks of aortic valve surgery and late complications of aortic valve prosthesis need to be balanced against the possibility of preventing sudden death and lowering cardiac mortality. We prospectively evaluated 197 consecutive asymptomatic patients with very severe aortic stenosis to compare clinical outcomes of early surgery with those of the conventional treatment strategy. Very severe aortic stenosis was defined as a critical stenosis in the aortic valve area \(\leq0.75\ \text{cm}^2\) accompanied by a peak aortic jet velocity \(\geq4.5\ \text{m/s}\) or a mean transaortic pressure gradient \(\geq50\ \text{mm Hg}\) on Doppler echocardiography. Early surgery was performed on 102 patients, and a conventional treatment strategy was used for 95 patients. There were no operative deaths and no cardiac deaths in the early surgery group compared with 18 cardiac deaths in the conventional treatment group, and the risk of all-cause mortality was significantly lower in the early surgery group than in the conventional treatment group (hazard ratio, 0.135; 95% confidence interval, 0.030–0.597; \(P=0.008\)). Compared with the conventional treatment strategy, early surgery is associated with improved long-term survival by effectively decreasing cardiac mortality and sudden cardiac death. This result suggests that early surgery can be a therapeutic option to further improve clinical outcomes in asymptomatic patients with very severe aortic stenosis and low operative risk. A prospective randomized trial is required to confirm the efficacy of early surgery.

**Conclusions:** Compared with the conventional treatment strategy, early surgery in patients with very severe aortic stenosis is associated with an improved long-term survival by decreasing cardiac mortality. Early surgery is therefore a therapeutic option to further improve clinical outcomes in asymptomatic patients with very severe aortic stenosis and low operative risk.\(^4\)

**Transcatheter Valve-in-Valve Implantation for Failed Bioprosthetic Heart Valves**

**Summary:** The majority of prosthetic heart valves currently implanted are tissue valves that can be expected to degenerate with time and eventually fail. Repeat cardiac surgery to replace these valves is associated with significant morbidity and mortality. Transcatheter heart valve implantation within a failed bioprosthesis, a “valve-in-valve” procedure, may offer a less invasive alternative. Valve-in-valve implantations were performed in 24 high-risk patients. Failed valves were aortic (\(n=10\)), mitral (\(n=7\)), pulmonary (\(n=6\)), or tricuspid (\(n=1\)) bioprostheses. Implantation was successful with immediate restoration of satisfactory valve function in all but 1 patient. No patient had more than mild regurgitation after implantation. No patients died during the procedure. Thirty-day mortality was 4.2%. Mortality was related primarily to learning-curve issues early in this high-risk experience. New York Heart Association functional class improved in most patients. At a median follow-up of 135 days and a maximum follow-up of 1045 days, 91.7% of patients remained alive with satisfactory valve function. Transcatheter valve-in-valve implantation is a reproducible option for the management of bioprosthetic valve failure. Aortic, pulmonary, mitral, and tricuspid tissue valves were amenable to this approach. This finding may have important implications with regard to valve replacement in high-risk patients.\(^5\)

**Effects of Mitral Valve Surgery on Myocardial Energetics in Patients With Severe Mitral Regurgitation**

**Summary:** Hemodynamically significant mitral regurgitation (MR) may alter left ventricular (LV) myocardial energy requirements. The effects of MR and subsequent corrective mitral valve (MV) surgery on myocardial energetics are not well understood. A better understanding of myocardial energetics and the LV responses to changes in preload and afterload may assist with the understanding of MR and its effect on the LV. We sought to determine the effects of MV surgery on forward stroke work, myocardial oxidative metabolism, and myocardial efficiency. Prospectively enrolled patients with chronic, severe, nonischemic MR underwent echocardiography, radionuclide angiography, and C-11 acetate positron emission to-mography to measure LV volumes, ejection fraction, oxidative metabolism, and work metabolic index before and 1 year after MV surgery. One year after MV surgery, there was a reduction in LV end-diastolic and end-systolic volumes, preservation of LV ejection fraction, and a conservation of total work metabolic index.

**Conclusions:** MV surgery has a beneficial effect on forward stroke volume and forward work metabolic index without adverse effects on oxidative metabolism or total work metabolic index.\(^6\)

**Combined Mitral and Tricuspid Valve Repair in Rheumatic Valve Disease: Fewer Reoperations With Prosthetic Ring Annuloplasty**

**Summary:** This study with very long-term results shows, probably for the first time, that in patients undergoing either mitral or tricuspid valve repair when both lesions have a rheumatic origin, the results obtained are more favorable with the use of a prosthetic ring annuloplasty. Implantation of a prosthetic ring in the mitral or tricuspid position was associated with significantly fewer valve dysfunction–related reoperations and a longer reoperation-free survival. As a result of this finding, mitral valve repair using percutaneous balloon dilatation of the valve might be a suboptimal technique. On the other hand, the historical comparison of patients with double rheumatic valve disease (mitral and tricuspid) treated with prosthetic mitral valve replacement confirms, even at very long-term follow-up, that mitral repair offers a better alternative with longer survival and fewer valve dysfunction reoperations. The present study is the largest experience of surgical treatment of rheumatic mitral/tricuspid valve disease with the longest follow-up. Although rheumatic disease is eradicated in the developed world, rheumatic fever is still the first cause of heart valve disease in 5 million people around the world.

**Conclusions:** Combined mitral and tricuspid valve repair in rheumatic disease showed satisfactory early results. Long-term results were poor because of high mortality and a high number of valve-related reoperations. The use of prosthetic ring annuloplasty was significantly associated with a reduced incidence of both mitral and tricuspid valve reoperations.\(^7\)

**Effect of Hydroxymethylglutaryl Coenzyme-A Reductase Inhibitors on the Long-Term Progression of Rheumatic Mitral Valve Disease**

**Summary:** This is the first study to assess the role of statin treatment in slowing the progression of rheumatic mitral stenosis (MS). Three hundred fifteen patients with rheumatic MS, either statin treated (35 patients, 11.1%) or untreated (280 patients, 88.9%), were followed for 6.1±4.0 years in this retrospective study. We found a significantly slower progression of MS, as assessed by decrease in mitral valve area, in patients treated with statins compared with untreated patients (0.027±0.056 versus 0.067±0.082 cm\(^2\)/yr; \(P=0.005\)). The increase in mean transmural gradient was also lower in statin-treated patients (0.20±0.59 versus 0.58±0.96 mm Hg/yr; \(P=0.023\)). The
prevalence of fast MS progression (annual change in mitral valve area $>0.08 \text{ cm}^2$) was significantly lower in the statin group ($P=0.008$). In addition, there was a significant effect of statin treatment in reducing progression of mitral regurgitation during follow-up ($P=0.038$). These results indicate a possible benefit of statin treatment in slowing the progression of rheumatic mitral valve disease. Although the global prevalence of rheumatic valve disease seems to be decreasing, this condition remains an important cause of morbidity and mortality in many areas of the world. A medical treatment effective in slowing the progression of rheumatic mitral valve disease would have a critical role in delaying mitral valve interventions (eg, percutaneous or surgical). This could be particularly important in areas where access to such interventions is inadequate. If confirmed by prospective randomized controlled trials, these results may have important therapeutic, social, and economic implications.

Conclusions: Our study shows a significantly slower progression of rheumatic MS in patients treated with statins. These findings could have an important impact in the early medical therapy of patients with rheumatic heart disease.8

Survival of Kidney Transplantation Patients in the United States After Cardiac Valve Replacement

Summary: Valvular heart disease is common in patients with end-stage renal disease. In hemodialysis patients, use of bioprosthetic heart valves was proscribed in past American College of Cardiology/American Heart Association guidelines, reflecting a widely held (but poorly substantiated) perception that bioprosthetic valve failure mandated mechanical prosthetic valves in these patients. In 2006, revised practice guidelines rescinded the proscription. Estimated 2-year mortality of dialysis patients is 60% after heart valve replacement surgery, with no difference in survival for tissue versus nontissue valves. Data on long-term survival of kidney transplantation patients after cardiac valve replacement are few. In this study, we identified 1335 kidney transplantation patients receiving left-sided cardiac valve replacement from 1991 to 2004. Use of tissue valves increased over time (28% overall, 38% in 2000–2004). Mortality risk associated with use of tissue (versus nontissue) valves was minimally reduced. In-hospital mortality was 14.0% overall, 11.4% for tissue-valve patients, and 15.0% for nontissue-valve patients ($P=0.09$), and estimated 2-year survival was 61.5% for tissue-valve and 59.5% for nontissue-valve patients ($P=NS$). The adjusted hazard ratio of death for tissue-valve versus nontissue-valve patients was 0.83 (95% confidence interval, 0.70–0.99). Hospitalizations for endocarditis and gastrointestinal hemorrhage were common (≈5%/yr) but not related to valve type. Regardless of the prosthetic valve type, overall 2-year mortality of renal transplantation patients after left-sided cardiac valvular replacement is 40%. The additional requirement for long-term anticoagulation with nontissue valves might support the preferential use of tissue valves by clinicians and their patients who wish to avoid warfarin therapy.

Conclusions: Renal transplantation patients requiring valve replacement have high mortality rates (≈20%/yr). These data suggest minimally reduced mortality risk for patients receiving tissue versus nontissue valves.9

Exercise Pulmonary Hypertension in Asymptomatic Degenerative Mitral Regurgitation

Summary: Current American College of Cardiology/American Heart Association and European Society of Cardiology guidelines recommend mitral valve surgery for asymptomatic patients with severe degenerative mitral regurgitation and preserved left ventricular systolic function when atrial fibrillation or pulmonary hypertension (PHT) is present. The American College of Cardiology/American Heart Association guidelines state that mitral valve surgery is reasonable in such patients in the presence of exercise PHT (defined as a systolic pulmonary arterial pressure $>60 \text{ mm Hg}$, Class IIa, Level of Evidence C). In this study, 78 consecutive asymptomatic patients with preserved left ventricular systolic function and moderate or severe mitral regurgitation were submitted to resting and exercise echocardiography. The results show that exercise PHT is frequent, is related to exercise mitral regurgitation severity, and is associated with 3.4-fold increase in the risk of development of symptoms. The best cutoff value of exercise systolic pulmonary arterial pressure was 56 mm Hg, which is close to the empirical threshold of 60 mm Hg used in the American College of Cardiology/American Heart Association guidelines. We found that exercise PHT is more accurate than resting PHT for predicting symptoms. Hence, exercise echocardiography appears to be useful in patients with asymptomatic degenerative mitral regurgitation for revealing the increase in mitral regurgitation severity and the presence of PHT during exercise and thus identifying patients at risk of developing symptoms rapidly. Close follow-up (3–6 months) is advised in asymptomatic patients developing exercise PHT. Prompt surgery to prevent adverse left atrial remodeling, irreversible left ventricular damage, and morbid events could potentially be indicated in these patients. On the other hand, a strategy of watchful waiting seems to be more appropriate in patients without exercise PHT.

Conclusions: Exercise PHT is frequent in patients with asymptomatic degenerative mitral regurgitation. Exercise mitral regurgitation severity is a strong independent predictor of both exercise systolic pulmonary arterial pressure and exercise PHT. Exercise PHT is associated with markedly low 2-year symptom-free survival, emphasizing the use of exercise echocardiography. An exercise systolic pulmonary arterial pressure $>56 \text{ mm Hg}$ accurately predicts the occurrence of symptoms.10

Association of Left Atrial Endothelin-1 With Atrial Rhythm, Size, and Fibrosis in Patients With Structural Heart Disease

Summary: Atrial fibrillation (AF) increases risk of stroke, morbidity, and mortality. Current treatments have significant limitations. Studies that identify pathways by which we can prevent the development or progression of AF may lead to improved treatment. AF imposes a metabolic and hemodynamic strain on the atria. At the same time, increased hemodynamic burden on the atria (as a result of hypertension, mitral regurgitation or heart failure) promotes atrial enlargement and fibrosis, a substrate for AF. Left atrial (LA) enlargement is associated with poor clinical outcomes. Endothelin-1 (ET-1), a well-known vasoconstrictor peptide with mitogenic properties, is increased in the plasma of AF patients with underlying structural heart disease. In this study, both ET-1 gene expression and processing were enhanced in the LA of AF patients, and increased content was associated with increased LA size and volume. More broadly, atrial ET-1 content is increased in conditions associated with increased LA hemodynamic burden. ET-1 levels were associated with AF persistence. Atrial ET-1 mRNA levels were correlated with the mRNA expression of fibrotic mediators (platelet-derived growth factor and connective tissue growth factor), as well as with the atrial mRNA expression of brain natriuretic peptide, a predictor of AF. These associations suggest that ET-1 may promote atrial enlargement and fibrosis and contribute to increased AF persistence. It would be of interest to determine if agents or procedures that reduce ET-1 production or block its receptors have a therapeutic benefit with respect to prevention of AF or slowing its progression.

Conclusions: Elevated atrial ET-1 content is associated with increased LA size, AF rhythm, hypertension, and heart failure. ET-1 is associated with atrial dilatation, fibrosis, and hypertrophy and probably contributes to AF persistence. Interventions that reduce atrial ET-1 expression and/or block its receptors may slow AF progression.11
Prevalence, Characteristics, and Outcomes of Patients Presenting With Cardiogenic Unilateral Pulmonary Edema

**Summary:** Cardiogenic bilateral pulmonary edema usually appears on chest x-rays as bilateral and symmetrical opacities, resulting in the classic “butterfly shadow.” Cardiogenic unilateral pulmonary edema (UPE) is an unusual entity. Little is known about the characteristics of UPE, and its prevalence has never been assessed in a large series of pulmonary edema. Among a large population with cardiogenic pulmonary edema (n = 869), we found that the prevalence of the unilateral pattern of cardiogenic pulmonary edema was 2.1%; that UPE was right-sided in 89%, involving mainly the right upper lobe; and that UPE was always associated with severe organic or functional mitral regurgitation. In-hospital mortality of UPE was significantly higher (39% versus 8% in patients with bilateral pulmonary edema). In multivariate analysis, UPE was independently related to death, with a risk of death 6.5-fold higher than in patients with bilateral pulmonary edema. Because of initial misdiagnosis caused by the unilateral location of opacities on chest x-rays, a delay in diagnosis and adequate treatment was observed in 33% of cases. These results have implications in routine practice to best recognize this clinical entity and thus to avoid delay in treatment that may affect prognosis.

**Conclusions:** Unilateral pulmonary edema represented 2.1% of cardiogenic pulmonary edema in our study, usually appeared as an opacity involving the right lung, and was always associated with severe mitral regurgitation. Unilateral pulmonary edema is related to an independent increased risk of mortality and should be promptly recognized to avoid delays in treatment.12

Spectrum and Outcome of Reoperations After the Ross Procedure

**Summary:** Although this manuscript deals with a topic that is surgical in nature, it also provides valuable information to cardiologists, because they are involved in the preoperative consultation and the long-term follow-up of patients being considered for the Ross procedure. The Ross procedure is performed for aortic valve disease and is offered to patients in all age groups: infants, children, and adults. The operation is palliative, and the need for reintervention (percutaneous or surgical) over a lifetime is inevitable for the majority of patients. This study represents the largest reported series of patients undergoing reoperation after the Ross procedure to date. Although literature is available that quantifies the incidence of reoperation after the Ross procedure, there are no published reports that address the qualitative nature and risks associated with reoperation when it is required. This manuscript provides that “missing” information so the clinician can properly counsel patients not only about the potential need for reoperation but also about the nature of the reoperation when it is necessary.

**Conclusions:** A broad spectrum of complex reoperations may be required after the Ross procedure. Patients and family members considering the procedure should be informed of the potential for associated morbidity should reoperation be necessary.13

In Vivo Measurement of Mitral Leaflet Surface Area and Subvalvular Geometry in Patients With Asymmetrical Septal Hypertrophy: Insights Into the Mechanism of Outflow Tract Obstruction

**Summary:** Dynamic left ventricular outflow tract obstruction (LVOTO) has long been recognized as a central feature of hypertrophic cardiomyopathy. Analyzing the determinants of systolic anterior motion of the mitral valve and consequent LVOTO in patients with asymmetrical septal hypertrophy requires a comprehensive 3-dimensional analysis of mitral leaflet area, papillary muscle (PM) geometry, and distribution of left ventricular hypertrophy. This study used real-time 3-dimensional echocardiography to demonstrate that patients with asymmetrical septal hypertrophy and LVOTO have larger mitral leaflet areas and shorter inter-PM distance. Determinants of minimal LVOT area during systole were end-systolic volume, indexed total mitral leaflet area, inter-PM distance, annular height, and LVOT hypertrophy index. These findings support the concept that myocardium is not the only tissue affected in patients with asymmetrical septal hypertrophy, and integrated PM–mitral valve geometry best explains the pathogenesis of LVOTO in patients with asymmetrical septal hypertrophy, with increased mitral leaflet area and annular height allowing greater leaflet slack, and PM position and LVOT hypertrophy positioning the slack leaflet into left ventricular outflow. Because each element of PM–mitral valve geometry can be thoroughly evaluated with the use of real-time 3-dimensional echocardiography, an individualized strategy can be applied accordingly, and primary changes of the mitral leaflet and subvalvular apparatus can be potential targets of new treatment options for effective relief of LVOTO.

**Conclusions:** Myocardium is not the only tissue affected in patients with asymmetrical septal hypertrophy, and primary changes of the mitral apparatus, including mitral leaflet area increase and PM displacement, are independent determinants of LVOT obstruction and provide a comprehensive mechanism that determines leaflet slack and anteriorly directed motion. Abnormal PM–mitral valve geometry assessed by real-time 3-dimensional echocardiography can provide reasonable new targets for individualized intervention.14

Anomalous Mitral Arcade in Twin–Twin Transfusion Syndrome

**Summary:** Twin–twin transfusion syndrome is an important cause of perinatal mortality in monochorionic twins, often because of cardiovascular compromise associated with increased intravascular volume in the recipient twin. In this autopsy study of 11 sets of twins with the condition, 4 recipient twins had anomalous mitral arcade, a rare fibrotic valve lesion that is associated with regurgitation. Previously unrecognized in twin–twin transfusion syndrome, anomalous mitral arcade may explain many of the progressive hemodynamic abnormalities in this condition. From this retrospective clinicopathological correlation study, ultrasound/echocardiographic evidence of left atrial dilation and significant mitral regurgitation in the recipient should raise suspicion for anomalous mitral arcade, a structural lesion that likely will not reverse after successful laser treatment or delivery of the fetus, as other hemodynamic and functional abnormalities often do. Thus, for perinatologists and fetal echocardiographers who manage patients with twin–twin transfusion syndrome, the present study suggests that acquired mitral arcade is likely a physiologically important lesion that may have prognostic significance in recipient twins. For pediatric cardiologists and scientists who study cardiac development, the occurrence of anomalous mitral arcade in this specific population and the progressive deterioration of hemodynamics in affected recipients militate against developmental arrest as the cause of the valve lesion. Anomalous mitral arcade likely represents a flow-related or acquired valve deformity, not a malformation.

**Conclusions:** Previously unreported in twin–twin transfusion syndrome, anomalous mitral arcade was identified in 4 of 11 recipient fetuses (36%) in this autopsy series. Ultrasound or echocardiographic evidence of left atrial dilation, mitral regurgitation, and decreased leaflet mobility in recipients should raise suspicion for anomalous mitral arcade. Development of anomalous mitral arcade in twin–twin transfusion syndrome recipients suggests that the lesion is an acquired valve deformity in this setting, not a malformation.15
Chymase Inhibition Prevents Fibronectin and Myofibrillar Loss and Improves Cardiomyocyte Function and LV Torsion Angle in Dogs With Isolated Mitral Regurgitation

Summary: The volume overload of isolated mitral regurgitation currently has no recommended therapy that improves left ventricular function or delays the need for surgery. Numerous studies in animal models have demonstrated extracellular matrix loss, rather than accumulation, in the pathophysiology of progressive left ventricular remodeling in a pure volume overload. Thus, blockade of the renin-angiotensin system has not proved successful in a situation of volume overload, in which collagen loss and cardiomyocyte slippage may occur early in the course of left ventricular remodeling. Chymase, in addition to formation of angiotensin II, can activate matrix metalloproteinases and directly degrade matricellular proteins important not only in connections to collagen but also in the initiation of detrimental intracellular signaling processes. Thus, blockade of chymase may prove to be an important therapeutic target in a pure volume overload.

Conclusions: These results suggest that chymase disrupts cell surface–fibronectin connections and FAK phosphorylation that can adversely affect cardiomyocyte myofibrillar structure and function. The greater effect of chymase inhibitor on epicardial versus endocardial titin and noncollagen cell surface proteins may be responsible for the increase in torsion angle in chronic mitral regurgitation.16

Anterior Mitral Leaflet Curvature During the Cardiac Cycle in the Normal Ovine Heart

Summary: Anterior mitral leaflet (AML) curvature dynamic changes are of primary importance for optimal left ventricular filling and emptying. Mitral leaflet curvature has been described in the closed position; however, dynamic leaflet curvature has not been characterized. With the increasing use of mitral valve repair techniques that substantially perturb the mitral leaflets (surgical or percutaneous edge-to-edge repair techniques), data describing the 3-dimensional geometry and curvature of the mitral leaflets throughout the cardiac cycle are needed. This in vivo ovine experiment used 4-dimensional tracking of a dense AML marker array coupled with a novel method of surface subdivision to quantify the changes in AML curvature. The septal-lateral curvature of the AML along the septal-lateral meridian was similar across the belly region at midsystole and early diastole; however, the commissure–commissure curvature of the commissure–commissure meridian changes, with the belly being convex to the left atrium at midsystole and concave at maximal valve opening. These findings suggest that the strut chordae may serve not only as anchors to preserve systolic and diastolic AML shape but also as hinge points for AML shape changes along the commissure–commissure meridian. Alteration of the shape of the leaflet could affect diastolic left ventricular filling and theoretically increase leaflet stresses during systole. These data suggest that the natural curvature of the AML produces optimal inflow and outflow shapes of the AML and should be preserved during catheter or surgical repair interventions.

Conclusions: While the septal-lateral curvature of the AML along the septal-lateral AML meridian is similar across the belly region at midsystole and early diastole, the commissure–commissure curvature of the AML along the commissure–commissure AML meridian flips, with the belly being convex to the left atrium at midsystole and concave at maximal valve opening. These curvature orientations suggest optimal left ventricular inflow and outflow shapes of the AML and should be preserved during catheter or surgical interventions.17

Dobutamine-Induced Improvement in Inferior Myocardial Contractile Function Predicts Reduction in Functional Mitral Regurgitation: A Study Using Tissue Doppler Strain Rate Imaging

Summary: Left ventricular (LV) remodeling can increase tethering of the mitral valve and be associated with functional mitral regurgitation (FMR). However, the relationship between FMR and regional myocardial function has not been quantitatively evaluated. The aim of this study is to conduct a quantitative investigation of this association at rest and with dobutamine using longitudinal systolic strain rate (Ssr) derived from tissue Doppler echocardiography as regional myocardial function. The effective regurgitant orifice (ERO) of FMR in 51 patients with depressed LV ejection fraction was compared with mitral deformation, global LV remodeling, and Ssr in 6 mid-LV segments. Multivariable analysis identified the predictors of ERO at rest as mitral valvular tenting, Ssr in the inferior segment (inferior Ssr), and LV sphericity and the predictors of valvular tenting at rest as inferior Ssr, LV end-systolic volume index, and LV sphericity. Furthermore, dobutamine-induced reduction in ERO was predicted by a reduction in valvular tenting and an increase in inferior Ssr, and dobutamine-induced reduction in valvular tenting was predicted by an increase in inferior Ssr. The results of this study suggest that inferior myocardial contractile function affects the configuration of mitral apparatus and predicts FMR severity. Dobutamine-induced improvement in myocardial function is known to predict improved function with medical treatment, and thus, dobutamine stress echocardiography could be used to predict improvement in FMR with appropriate treatment especially by assessing inferior contractile reserve. Furthermore, this test could be useful in predicting whether revascularization of viable myocardium in the inferior distribution might be associated with improvement in FMR.

Conclusions: Inferior regional myocardial dysfunction was quantitatively associated with mitral valvular tenting and FMR. Moreover, improvement with dobutamine of inferior myocardial contractile function attenuated valvular tenting and FMR. Inferior myocardial contractile function can affect the configuration of the mitral apparatus and predict FMR severity.18

Relief of Mitral Leaflet Tethering Following Chronic Myocardial Infarction by Chordal Cutting Diminishes Left Ventricular Remodeling

Summary: One of the key targets of reducing mitral regurgitation (MR) is the reduction of otherwise progressive left ventricular (LV) remodeling, which exacerbates MR and conveys adverse prognosis. Postinfarction, leaflet closure is restricted by tethering to displaced papillary muscles, with a prominent bend in the basal anterior leaflet (seagull sign) and markedly limited posterior leaflet motion (Carpentier functional classification type 3b). Chordal connections help to maintain normal contractile function but cause mitral leaflet tethering and ischemic MR following myocardial infarction. Chordal cutting relieves tethering and MR, but its effect on LV remodeling has needed testing. This study demonstrates that cutting secondary chordae to the anterior or both leaflets in the chronic myocardial infarction setting does not exacerbate long-term LV remodeling; it not only relieves MR, but also limits progressive increases in LV volumes. This study confirms the long-term safety of this technique, which has entered clinical applications, and its availability as a strategy to relieve both ischemic MR and LV remodeling.

Conclusions: Reduced leaflet tethering by chordal cutting in the chronic post–myocardial infarction setting substantially decreases the progression of LV remodeling with sustained reduction of MR over a chronic follow-up. These benefits have the potential to improve clinical outcomes.19
Changes in Mitral Annular Geometry and Dynamics With β-Blockade in Patients With Degenerative Mitral Valve Disease

Summary: Primary mitral regurgitation (MR), which usually is caused by myxomatous degeneration of the mitral valve (MV) leaflets, leads to a progressive increase in left ventricular (LV) volume. Eventually, this may result in LV dysfunction and heart failure. In patients with myxomatous MV disease, it has been shown previously that β-blockers reduced LV work and mitral regurgitant volume per minute, but the impact of β-blockers on MV annular dimensions and dynamics is uncertain. Twenty-five patients with moderate-to-severe degenerative MR and normal LV systolic function were studied in a double-blind crossover experiment using a β1-selective adrenergic blocker and placebo administered for 14±3 days. Cardiac MRI images were acquired after each treatment period, and mitral annular dimensions were quantified with semiautomated soft-tissue tracking software. Despite significant increases in LV end-diastolic and end-systolic volumes, short-term β-blocker treatment of patients with moderate-to-severe MR reduced or preserved the majority of mitral annular dimensions. This favorable effect of β-blockade on mitral annular dimensions, if maintained with longer-term treatment, combined with negative inotropic and chronotropic effects may reduce the progression of chronic MR.

Conclusions: Despite significant increases in LV end-diastolic and end-systolic volume, short-term β-blocker treatment of patients with moderate-to-severe MR reduced or preserved all mitral annular dimensions except septal-lateral at end systole.

Characterization of Degenerative Mitral Valve Disease Using Morphological Analysis of Real-Time Three-Dimensional Echocardiographic Images: Objective Insight Into Complexity and Planning of Mitral Valve Repair

Summary: Degenerative mitral valve disease (DMVD) frequently includes different degrees of annular dilation, leaflet redundancy, and chordal dysfunction, which result in variable cardiovascular morbidity and mortality. DMVD encompasses 2 broad categories, fibroelastic deficiency and Barlow disease. Accurate diagnosis of these entities along with their specific location and complexity is important because they require different surgical planning, which necessitates careful matching between the complexity of reparability and surgical expertise. Differential diagnosis in DMVD is challenging because it relies on qualitative evaluation that requires a high level of expertise. Quantitative decision support would be useful in assessing key anatomic features of DMVD and therefore guide appropriate surgical strategy. This is the first comprehensive study to characterize DMVD objectively using real-time 3D echocardiography. We sought to describe the pathomorphology of the MV in DMVD and to identify real-time 3D echocardiography parameters that can accurately characterize DMVD. Our results have yielded a systematic approach to differentiating DMVD from normal valves and importantly Barlow disease from fibroelastic deficiency before surgery. In the proposed algorithm, DMVD can be differentiated from normal valves based on billowing height, whereas billowing volume can be used to distinguish between Barlow disease and fibroelastic deficiency patients. Use of this quantitative algorithm makes early differentiation feasible and the diagnosis more objective and less experience-dependent, highlights quantitative anatomic differences between the groups, and provides a framework for preoperative assessment of the complexity of repair. As quantification tools become more automated and less reliant on expertise, they may be used to support clinical decision-making by a wider group of physicians.

Conclusions: Morphological analysis as a form of decision support in assessing mitral valve billowing revealed significant quantifiable differences between control, fibroelastic deficiency, and Barlow disease patients, allowing accurate classification of the etiology of mitral valve prolapse and determination of the anticipated complexity of repair.

Survival Comparison of the Ross Procedure and Mechanical Valve Replacement With Optimal Self-Management Anticoagulation Therapy: Propensity-Matched Cohort Study

Summary: Survival in young adult patients after mechanical aortic valve replacement is reported to be significantly reduced compared with the general age- and gender-matched population, whereas survival after the Ross procedure is excellent and comparable to that in the general population. There is ongoing debate about whether the excellent survival rates observed in Ross patients are a consequence of a hemodynamically superior valve and low valve-related complication rates or of patient selection. This is the first study to compare survival in young adult patients after mechanical aortic valve replacement and the Ross procedure using propensity score matching. In comparable patients, there was no late survival advantage in the first postoperative decade for the Ross procedure over mechanical aortic valve implantation with optimal anticoagulation self-management. In contrast to older reports, the relative survival in these selected young adult patients closely resembles that of the general population, possibly a result of better timing of surgery, improved patient selection, and highly specialized self-management anticoagulation treatment in more recent years. In the absence of late mortality differences between comparable patients who received either a mechanical prosthesis or the Ross procedure, the weight of the prosthetic valve selection decision making process shifts toward quality of life and patient preference. Clinicians are therefore encouraged to systematically elicit patient preferences when discussing prosthetic valve selection in this young adult population.

Conclusions: In comparable patients, there is no late survival difference in the first postoperative decade between the Ross procedure and mechanical aortic valve implantation with optimal anticoagulation self-management. Survival in these selected young adult patients closely resembles that of the general population, possibly as a result of highly specialized anticoagulation self-management, better timing of surgery, and improved patient selection in recent years.

Pathological Healing Response of Explanted MitraClip Devices

Summary: Mitral regurgitation remains one of the most common forms of valvar heart disease. Available treatment options have been limited to surgical repair or replacement. However, many patients are elderly, with coexisting conditions that preclude surgery. The MitraClip is a novel percutaneous device that uses a catheter-based system to create a double-orifice mitral valve, thereby reducing mitral regurgitation. The device has been implanted in 337 patients in the Endovascular Valve Edge-to-Edge Repair Study (EVEREST) I and EVEREST II (prerandomization, randomized pivotal study, and high-risk registry) clinical trials for correction of degenerative and functional mitral regurgitation. It was designed to allow removal and conversion to surgery if clinically warranted at any time after device implantation. To date, our laboratory has received 67 explanted devices from 50 patients for pathological analysis. Importantly, this is the first pathological study to report on the gross and histological features observed in the explanted devices at durations of up to 5 years. Analysis of the explants and tissue response provided insights into the time course of healing and documented mechanical stability over time. In addition, the data were stratified between patients with degenerative versus functional mitral regurgitation to elucidate potential differences in healing between these 2 very different disease entities. From the information gleaned from this study, we concluded that factors other than device healing likely explained the persistence or return of mitral regurgitation in this group of explanted patients. Ultimately, the formation
Mechanisms of Acute Mitral Regurgitation in Patients With Takotsubo Cardiomyopathy: An Echocardiographic Study

Summary: Despite the favorable outcome of takotsubo cardiomyopathy (TTC) in general, the presence of significant acute mitral regurgitation (MR) increases the risks of acute deterioration and adverse outcome in TTC. However, the mechanism of acute MR in TTC remains unclear. In this study, we elucidated the mechanisms of acute MR in TTC: apical tethering and systolic anterior motion of the mitral valve are 2 independent mechanisms that can lead to acute MR in TTC. Our finding of simultaneous improvement of apical tethering and MR severity in the patients with TTC is particularly important for the understanding of the mechanism of acute MR. Based on the study results, TTC should be regarded as a potential cause of acute MR. In addition, pulmonary artery systolic pressure is significantly higher in patients with TTC with MR than in those without MR. Therefore, early detection of MR is important for proper management of patients with TTC. The current American College of Cardiology/American Heart Association guidelines recommend mitral valve surgery in symptomatic patients with severe acute MR; however, the present results support the idea that aggressive medical treatment of TTC would be the first priority because acute MR in TTC is reversible. These findings imply that echocardiography should be systematically performed in patients with TTC to identify MR and assess its mechanism.

Conclusions: Systolic anterior motion of the mitral valve and tethering of the mitral valve are independent mechanisms with differing pathophysiology that can lead to acute MR in patients with TTC.

Mitral Valve Abnormalities Identified by Cardiovascular Magnetic Resonance Represent a Primary Phenotypic Expression of Hypertrophic Cardiomyopathy

Summary: Mutations in genes encoding proteins of the cardiac sarcomere are responsible for left ventricular hypertrophy, the diagnostic sine qua non of hypertrophic cardiomyopathy (HCM). However, whether other morphological features of HCM, seemingly unrelated to sarcomere mutations, are part of the disease phenotype is uncertain. We used cardiovascular magnetic resonance to characterize mitral valve abnormalities in a cohort of patients with HCM. Both anterior and posterior mitral valve leaflet lengths were greater among HCM patients compared with an age- and sex-matched control population (26.5 vs. 19.2 ± 5 mm, P < 0.001; and 14.2 ± 4 versus 10 ± 3 mm, P < 0.001, respectively), including more than one third of HCM patients in whom one or both of the mitral leaflets were substantially increased in length. In HCM patients, there was no relationship between mitral valve leaflet length and a number of clinical and demographic variables, including age, maximal left ventricular wall thickness, or left ventricular mass. In addition, elongated mitral valve leaflets were often the only clinical manifestation present in HCM family members carrying a sarcomere mutation without left ventricular hypertrophy and can represent the sole clinical marker of genotype-positive status. Elongated mitral valve leaflets were an important determinant of left ventricular outflow obstruction, particularly in patients in whom anterior mitral leaflet length exceeded 2-fold the transverse dimension of the outflow tract. These cardiovascular magnetic resonance–based observations show that structural abnormalities of the mitral valve represent a primary expression of the HCM phenotype and a morphological marker that may aid in diagnostic and management strategies, including optimal planning for septal reduction therapy.

Conclusions: In HCM, mitral valve leaflets are elongated independently of other disease variables, likely constituting a primary phenotypic expression of this heterogeneous disease, and are an important morphological abnormality responsible for left ventricular outflow obstruction in combination with small outflow tract dimension. These findings suggest a novel role for cardiac magnetic resonance in the assessment of HCM.

Cardiac Resynchronization Therapy as a Therapeutic Option in Patients With Moderate–Severe Functional Mitral Regurgitation and High Operative Risk

Summary: In heart failure patients with ischemic or nonischemic cardiomyopathy, functional mitral regurgitation (MR) is a frequent finding that has important prognostic implications. Functional MR can be treated surgically by means of restrictive annuloplasty with or without additional surgical left ventricular remodeling. However, the beneficial effect of this procedure on long-term mortality has not been clearly demonstrated, and many of these patients may not be referred for or are denied mitral valve surgery because of the high operative mortality risk. The current study sought to investigate the effect of cardiac resynchronization therapy (CRT) on moderate–severe functional MR and whether the reduction in severity of MR after CRT positively influenced long-term prognosis (survival). In 85 heart failure patients with moderate–severe functional MR, a significant reduction in extent of MR was observed after CRT, and particularly 42 patients (49%) improved ≥1 grade of MR. Importantly, improvement in MR was a strong independent prognostic factor of improved survival (hazard ratio, 0.35, P = 0.043). These findings demonstrate that CRT may improve MR in heart failure patients with moderate–severe functional MR and high risk for surgery. Secondly, the current study showed for the first time that the improvement in MR results in superior survival during long-term follow-up independently of other known prognostic factors. Therefore, CRT may yield a valuable therapeutic option for heart failure patients with moderate–severe functional MR but with a high operative risk.

Conclusions: Cardiac resynchronization therapy is a potential therapeutic option in heart failure patients with moderate–severe functional MR and high risk for surgery. Improvement in MR results in superior survival after CRT.

In Vitro Characterization of the Mechanisms Responsible for Functional Tricuspid Regurgitation

Summary: Current repairs for functional tricuspid regurgitation (TR) focus mainly on reducing the size of the annulus to correct annular dilatation and often result in recurrent TR, requiring additional treatment. We believe that understanding the mechanisms responsible for TR will lead to improved diagnosis and treatment. Although it is accepted that annuloplasty is beneficial in the correction of TR, this study shows that it may also be important to restore the available leaflet length for coaptation, providing as much overlap as possible, specifically in the central region. In the presence of papillary muscle displacement, reducing the annulus to its normal size with a ring annuloplasty may not be enough if the papillary muscles are displaced enough to severely affect the mechanics of proper leaflet closure. With evidence that papillary muscle displacement alone can lead to TR, it may be important to investigate papillary muscle position and ventricular size, both right and left, in addition to annulus area when the physician decides on the technique for tricuspid valve repair. More specifically, evidence-based standards...
are ultimately needed to ensure that those who need treatment are treated appropriately. As more research is conducted to understand the mechanisms of TR, these thresholds and possibly even predictors may be discovered.

Conclusions: This study shows that although annular dilatation alone leads to TR, isolated papillary muscle displacement can also cause TR; annular remodeling strategies should be tailored in the setting of severe papillary muscle displacement.27

Left Atrial Size Is a Potent Predictor of Mortality in Mitral Regurgitation Due to Flail Leaflets: Results From a Large International Multicenter Study

Summary: LA enlargement is common in chronic MR and is emerging as an important prognostic marker. However, the outcome implications of LA enlargement have not been analyzed in the context of routine clinical practice and in a multicenter study. The present analysis of the MIDA registry aimed to establish whether LA diameter, a simple measure of LA enlargement, is predictive of mortality under medical treatment and after mitral surgery in patients with organic MR due to flail leaflets. The relation between LA diameter and mortality was studied in 788 patients in sinus rhythm followed for 6.2 ± 3.9 years. LA diameter was independently associated with survival after diagnosis (HR, 1.08 [1.04–1.12] per 1-mm increment). The optimal cutoff value for prediction of mortality identified by receiver operating characteristic curve analysis was 55 mm. LA diameter ≥ 55 mm was associated with more than 3-fold increase in the risk of overall and cardiac mortality under medical treatment. The association of LA diameter ≥ 55 mm and mortality was consistent in subgroups of patients with MR and similar excess mortality was observed in asymptomatic and symptomatic patients. In patients who underwent mitral surgery, LA diameter ≥ 55 mm had no independent impact on postoperative outcome. Our findings show that LA diameter is a simple measurement that might improve risk stratification and decision making in chronic organic MR. LA diameter ≥ 55 mm is associated with increased mortality under medical treatment, independent of the presence of symptoms or left ventricular dysfunction.

Conclusions: In MR caused by flail leaflets, LA diameter ≥ 55 mm is associated with increased mortality under medical treatment, independent of the presence of symptoms or left ventricular dysfunction.28

Echocardiographic Variables After Left Ventricular Assist Device Implantation Associated With Adverse Outcome

Summary: A successful acute outcome after left ventricular assist device (LVAD) implantation depends on patient selection and the technical difficulty of surgery. However, how we treat our patients and LVAD settings may affect the patient outcome beyond the postsurgical period. In the present study, we retrospectively analyzed various variables in echocardiographic examinations performed 30 days after LVAD implant for their association with a compound end point (90-day mortality, readmission for heart failure, or New York Heart Association class III or higher at the end of the 90-day period). We found that mortality and persistent heart failure after LVAD surgery are predominantly associated with echocardiographic variables assessing the efficiency of unloading of the left ventricle and atrium, and those assessing right ventricular function. The only right ventricular variable significantly associated with adverse outcome was a decreased tissue Doppler velocity of the lateral tricuspid annulus. The variables assessing LV unloading, associated with adverse outcome were a high estimated left atrial pressure (> 15 mm Hg) and a short mitral inflow deceleration time divided by the E wave velocity (< 2 m/s/cm/s). An interventricular septum deviated to the left was associated with worse outcome as well. In conclusion, echocardiographic variables suggestive of efficient but not excessive LV unloading are associated with favorable mid and long-term outcome after LVAD surgery.

Conclusions: Mortality and heart failure after LVAD surgery appear to be predominantly determined by echocardiographic evidence of inefficient unloading of the left ventricle and persistence of right ventricular dysfunction. Increased estimated left atrial pressure and short mitral deceleration index are associated with worse midterm outcome. Leftward deviation of the septum is associated with worse outcome as well.29

Short-Term Performance of the Transcatheter Melody Valve in High-Pressure Hemodynamic Environments in the Pulmonary and Systemic Circulations

Summary: The Melody valve is approved for percutaneous pulmonary valve replacement in dysfunctional right ventricular outflow tracts. The functioning of this valve in a low-pressure environment is well established. This initial small series describes the unique use of the Melody valve in the high-pressure environment of the aortic and mitral valves. Short-term follow-up of the Melody valve in a high-pressure environment demonstrates good valve function over 1 year.

Conclusions: Short-term performance of the Melody valve in high-pressure environments is encouraging, with good valve function in all patients.30

References
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