Left Atrial Function in Diastolic Heart Failure

**Summary:** The underlying pathophysiological mechanisms for the transition from an asymptomatic state of diastolic dysfunction to one of diastolic heart failure (DHF) are poorly defined. A noninvasive index that can help identify patients with DHF from those with asymptomatic diastolic dysfunction is of clinical interest. This study compared several parameters of left atrial (LA) and left ventricular (LV) function and arterial elastance between patients with DHF and diastolic dysfunction. LV volumes, mass, and systolic function were not significantly different between the 2 groups. Likewise, LA volumes and noninvasive measurements of LA systolic function, as well as arterial elastance, were similar in patients with DHF and those in the diastolic dysfunction group. On the other hand, LA stiffness was significantly lower in patients with DHF, and LA stiffness, both by invasive and noninvasive estimates, was significantly higher. LA stiffness was strongly correlated with the pulmonary artery systolic pressure and was the most accurate parameter in differentiating patients with DHF from diastolic dysfunction.

**Conclusions:** Patients with DHF have increased LV mass and LA volume in comparison with normal control subject but not versus patients with LV hypertrophy who are not in heart failure. On the other hand, LA strain is significantly reduced, and LA stiffness is the most accurate index in identifying patients with DHF.

**Editor’s Comment:** Although echo-Doppler methods for assessing left ventricular diastolic function are well established, the link between diastolic dysfunction and diastolic heart failure is less clearly defined. In this study, the authors report that left atrial strain is reduced in patients with diastolic heart failure as compared with those with diastolic dysfunction without heart failure and that a measure of left atrial stiffness (pulmonary capillary wedge pressure/LA strain) was accurate in distinguishing between these 2 groups. LA stiffness also correlated well with pulmonary artery systolic pressure. LA stiffness and LA strain have the potential to be clinically useful tools in assessing patients with suspected heart failure on the basis of diastolic dysfunction.

A Study of Functional Anatomy of Aortic-Mitral Valve Coupling Using 3D Matrix Transesophageal Echocardiography

**Summary:** To date, several imaging modalities have been used to separately study the functional anatomy of the aortic and mitral valve. However, the coupling between the aortic and mitral valves in 3D was studied only in animals through the use of invasive markers. In humans, the newly developed transesophageal real-time 3D echocardiography is increasingly playing an important role in the assessment of functional anatomy of these valves. To our knowledge, this is the first study to develop and test a noninvasive technique for detailed characterization of aortic valve dynamics and quantitative evaluation of mitral and aortic valvular coupling throughout the cardiac cycle in a beating human heart with the use of this new technology. Our results demonstrate the potential of this methodology to quantify parameters describing aortic and mitral valve functional anatomy in 3 dimensions and their coupling. Our findings underscore the need to consider the aortic and mitral valves jointly rather than as separate entities, not only because they are linked anatomically but also because the dynamic changes in their shape and position are reciprocally correlated. This technology will allow the assessment of the impact of a variety of mitral and aortic rings on the annular dynamics.

**Conclusions:** This is the first study to report quantitative 3D assessment of the mitral and aortic valve dynamics from matrix-array transesophageal images and describe the mitral-aortic coupling in a beating human heart. This ability may have an impact on patient evaluation for valvular surgical interventions and prosthesis design.

**Editor’s Comment:** The interaction between the aortic and mitral valves attributable to their connection through the fibrous aortic-mitral curtain is increasingly recognized as an important determinant of valvular function. In this study, 3D transesophageal echocardiographic volumes were analyzed, using prerelease software to address aortic-mitral valvar coupling. Reciprocal changes in mitral annular surface area and aortic annular projected area as well as a dynamically changing aortic-mitral annular angle were reported. Although this study was limited to subjects with normal valves, the technology has the potential to be a valuable tool for studying changes in aortic-mitral coupling due to interventions on one or both valves.

Reduced Systolic Torsion in Chronic “Pure” Mitral Regurgitation

**Summary:** Uncorrected chronic ischemic mitral regurgitation (CIMR) is associated with decreased left ventricular (LV) torsion and may contribute to a vicious cycle wherein “MR begets MR.” It has not been definitively established, however, whether the reduced LV torsion in CIMR is a direct result of the infarct, the MR, or a combination of the two. Currently, the most common technique to restore valve competence in patients with CIMR is the placement of an undersized annuloplasty ring. There exists, however, an ongoing debate about whether or not mitral valve annuloplasty at the time of coronary artery bypass grafting (CABG) improves outcomes over and above CABG alone. Hypothetically, if the reduction in LV torsion can be attributed to MR alone, then mitral valve repair...
concomitant with CABG may be important for minimizing the deterioration in LV torsion. Chronic “pure” MR was created in 13 sheep by surgically punching a 3.5- to 4.8-mm hole (HOLE) in the mitral valve posterior leaflet. Nine control (CNTL) sheep were operated on concurrently. At 1 and 12 weeks after surgery, the 4D motion of implanted radiopaque markers was used to calculate global LV torsion. Global LV systolic torsion decreased in HOLE from week 1 to week 12 (4.1±2.5° versus 1.7±1.7°, P<0.01) but did not change in CNTL (5.5±1.8° versus 4.2±2.7°, P=NS). These data suggest that in patients with CIMR, the MR itself may promote deterioration of LV torsion. MV repair in patients with CIMR concomitant with CABG may therefore help to slow down, stop, or even restore physiological LV torsion.

Conclusions: Twelve weeks of chronic “pure” MR resulting in mild global LV remodeling is associated with significantly increased LV mass index and reduced global LV systolic torsion but no other significant changes in hemodynamics. MR alone is a major component of torsional deterioration in “pure” MR and may be an important factor in chronic ischemic MR.

Editor’s Comment: Ventricular twist/torsion is recognized as an important element of ventricular function and has been shown to be impaired in chronic ischemic MR. However, the impact of chronic isolated (pure) MR on torsion has not been previously reported. In this ovine model in which MR was created by punching a hole in the posterior mitral leaflet, global LV systolic torsion, as measured by tracking the motion of radio-opaque markers, was shown to be reduced at 12 weeks. This argues that MR alone, without the ischemic LV dysfunction that characterizes ischemic MR, negatively affects LV torsion. This adds to our understanding of the pathobiology of MR.3

Relationships Among Regional Arterial Inflammation, Calcification, Risk Factors, and Biomarkers: A Prospective Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Imaging Study

Summary: Atherosclerotic plaque inflammation is thought to be central to plaque rupture and, by extension, clinical events such as acute coronary syndrome, stroke, and transient ischemic attack. By identifying such plaques before symptoms become apparent, preventive therapies such as statins might be initiated or intensified. Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET) is already established for cancer diagnosis, staging, and the prediction of tumor response to therapy. Our study applied this noninvasive imaging technology to atherosclerosis of the carotid, femoral, and iliac arteries and the aorta. We explored the links between plaque inflammation, arterial calcification, circulating biomarkers, and atherogenic risk factors. We found that there was strong symmetry in the distribution of arterial inflammation and that calcification was inversely linked with inflammation. We also confirmed previous work by demonstrating that arterial inflammation was greater in male patients and in those with a diagnosis of coronary artery disease. Clinical applications of this work may include the use of imaging for prediction of plaque rupture, insight into the pathobiology of atherosclerosis, and monitoring of antiatherosclerosis therapies. Underpinning these applications, studies are already underway that will link imaging findings with clinical events. In addition, FDG-PET atherosclerosis imaging is already being used as a surrogate marker of antiatherosclerotic drug efficacy by several pharmaceutical companies seeking to exploit its uniquely high sensitivity and reproducibility.

Conclusions: This study shows that FDG-PET imaging can increase our knowledge of how atherosclerotic plaque inflammation relates to calcification, serum biomarkers, and vascular risk factors. Plaque inflammation and calcification rarely overlap, supporting the theory that calcification represents a late, burnt-out stage of atherosclerosis. Inflammation in one arterial territory is associated with inflammation elsewhere, and the degree of local arterial inflammation is reflected in the blood levels of several circulating biomarkers. We suggest that FDG-PET imaging could be used as a surrogate marker of both atherosclerotic disease activity and drug effectiveness. Prospective, event-driven studies are now underway to determine the role of this technique in clinical risk prediction.

Editor’s Comment: There is a growing body of evidence supporting a potential role for molecular imaging strategies in the identification of high-risk atherosclerotic plaques. There is growing, consistent evidence from experimental and human studies that FDG-PET imaging may be a useful noninvasive marker of vascular inflammation. This study demonstrates that FDG accumulation differs across vascular beds of individuals with atherosclerosis and that the intensity of its uptake in the vessel wall correlates with circulating biomarkers of inflammation, further supporting its role as a potential biomarker of inflammation that can be imaged and quantified noninvasively with PET.4

Age-Related Left Ventricular Remodeling and Associated Risk for Cardiovascular Outcomes: The Multi-Ethnic Study of Atherosclerosis

Summary: Age-related alterations of left ventricular (LV) structure and function that may predispose to cardiovascular events are not well understood. Therefore, we used cardiac MRI to examine age-related differences in LV structure and function among 5004 participants of the Multi-Ethnic Study of Atherosclerosis, who had no cardiovascular disease at baseline; additional strain analyses were performed for 1099 of these participants. We also assessed the relation of age-associated remodeling with cardiovascular outcomes while adjusting for traditional risk factors. In multivariable regression models, age was associated with a decrease in LV mass but also marked increased in the LV mass-to-volume ratio driven by substantial reduction in LV end-diastolic volume. Age was also associated with a significant fall in stroke volume along with strain patterns reflecting systolic as well as diastolic myocardial dysfunction, despite a modestly enhanced ejection fraction. Higher mass-to-volume ratio conferred a significant risk for total cardiovascular events, and this trend was strongest among younger (age <65 years; hazard ratio, 3.69; P=0.011) versus older (age ≥65 years; hazard ratio, 1.68; P=0.190) individuals with the highest compared with lowest mass-to-volume ratio quintile (Pinteraction=0.013). These findings suggest that age is associated with a phenotype of LV remodeling marked by increased mass-to-volume ratio and accompanied by systolic as well as diastolic myocardial dysfunction that is not reflected by preserved ejection fraction. This pattern of ventricular remodeling appears to confer significant cardiovascular risk, especially when present earlier in life.

Conclusions: Age is associated with a phenotype of LV remodeling marked by increased mass-to-volume ratio and accompanied by systolic as well as diastolic myocardial dysfunction that is not reflected by preserved ejection fraction. This pattern of ventricular remodeling confers significant cardiovascular risk, particularly when present earlier in life.

Editor’s Comment: This large-scale, longitudinal cohort study of asymptomatic subjects provides unique and substantial evidence that an age-specific phenotype of LV remodeling characterized by increased mass-to-volume ratio in younger individuals confers a significantly increased cardiovascular risk, independent of sex and ethnicity. Future studies should put this finding in the context of blood biomarkers indicating myocardial stress and the presence of subclinical coronary artery disease. Such assessment would improve our understanding of the contribution of subclinical coronary artery disease to early alterations of myocardial function and would inform the formulation of sequential targeted screening strategies to identify intervention targets.5
Left Atrial Volume and Geometry in Healthy Aging: The Cardiovascular Health Study

**Summary:** Left atrial (LA) size is increased in a variety of cardiovascular disorders, and its enlargement is usually an indicator of chronically increased LA pressure and/or volume. Because the prevalence of LA enlargement increases with age, it is critical to have accurate normative reference ranges for heart sizes to correctly predict cardiovascular risk in the elderly. At present, there is a dearth of such reference data in population-based samples and in women. Accordingly, we have evaluated parameters of LA size in 230 healthy men and women (mean age, 76 ± 5 years) who were judged to be free of heart disease, hypertension, and diabetes. These subjects were a subset of the Cardiovascular Health Study, a prospective, community-based study of risk factors for cardiovascular disease conducted in 5888 elderly participants. We found that LA size is more strongly related to measures of body weight than to body height and developed a series of reference equations that predict what the normal LA dimensions and volumes should be, based on the subject’s age, height, and weight. We have also created somatograms that will enable clinicians to easily diagnose LA enlargement. We hope that these data can be used to help better determine what a normal LA size should be. An earlier diagnosis of LA enlargement might permit earlier preventive cardiology strategies in, for example, hypertensive disease.

**Conclusions:** These data provide normative reference values for LA size in healthy older women and men. The results should be useful for refining diagnostic criteria for LA dilation in the older population and may be relevant for cardiovascular risk stratification.

**Editor’s Comment:** This study introduces standardized estimates of LA volumes in healthy older women and men, based on standard 2D echocardiography. The data establish reference values for the elderly population and provide the basis for categorical risk assessment. With the growing availability of cardiac CT, comparison of these measurements to 3D volumetric assessments and outcomes is warranted. These data could be helpful to assess progression of LA dilation, for example, in patients with paroxysmal atrial fibrillation.

Evaluation of αvβ3 Integrin-Targeted Positron Emission Tomography Tracer 18F-Galacto-RGD for Imaging of Vascular Inflammation in Atherosclerotic Mice

**Summary:** The αvβ3 integrin is a cell-surface receptor that mediates cell-to-cell and cell-to–extracellular matrix connections. It can be highly expressed by macrophages and endothelial cells in atherosclerotic lesions. Therefore, it could serve as a biomarker of inflammation and neovascularization in atherosclerotic lesions, which have been implicated as risk factors for acute plaque rupture. 18F-Galacto-RGD is a positron emission tomography tracer for imaging the level of αvβ3 integrin expression. We demonstrate that 18F-galacto-RGD shows αvβ3 integrin-dependent uptake in atherosclerotic plaques in the aorta of hypercholesterolemic mice. Autoradiography of aortic tissue sections revealed higher 18F-galacto-RGD accumulation in the atherosclerotic plaques than in normal vessel wall. Plaque-to–normal vessel wall ratios were comparable to those of deoxyglucose. Although angiogenesis was not detected, 18F-galacto-RGD uptake was associated with macrophage density in the plaques. In vivo imaging visualized 18F-galacto-RGD uptake colocalizing with calcified lesions of the aortic arch, as seen on computed tomography angiography. The results indicate that 18F-galacto-RGD is a potential tracer for noninvasive imaging of inflammation in atherosclerotic lesions.

**Conclusions:** 18F-Galacto-RGD demonstrates specific uptake in atherosclerotic lesions of mouse aorta. In this model, its uptake was associated with macrophage density. 18F-Galacto-RGD is a potential tracer for noninvasive imaging of inflammation in atherosclerotic lesions.

Cardiac Mechanics in Mild Hypertensive Heart Disease: A Speckle-Strain Imaging Study

**Summary:** Clinical identification of high-risk hypertensive patients is desirable for preventive strategies. We hypothesized that abnormalities in regional systolic strain (e) may help identify such high-risk patients even when the ejection fraction is normal. Accordingly, the aim of the current study was to use echocardiographic speckle tracking imaging, a technique that is independent of ultrasound angle of interrogation, to identify subclinical global and regional systolic function abnormalities in hypertensive subjects with normal ejection fraction. Accordingly, 2D speckle-strain imaging was performed in 104 subjects (52 hypertensive subjects, 53 ± 12 years of age, and 52 control subjects, 49 ± 13 years of age; P = 0.82), all of whom had normal ejection fraction. We measured systolic velocities as well as systolic strains. Our principal findings were that when compared with control subjects, hypertensive subjects had lower myocardial systolic velocities but similar values for e in all 3 planes: longitudinal, radial, and circumferential. Among hypertensive subjects, significant inverse associations were found between left ventricular mass and global longitudinal (r = −0.51) and circumferential e (r = −0.21; both P < 0.05). To summarize, mild hypertensive heart disease with normal ejection fraction was associated with reduced myocardial systolic velocities but normal global e. We interpret these data as showing that velocity abnormalities occur early in hypertension, are related to ventricular geometry, and thus may be an appropriate target for preventive strategies because they occur before detectable abnormalities in global strain.

**Conclusions:** Hypertensive heart disease with normal ejection fraction is associated with reduced myocardial velocities and reduced regional function but normal global e. Our data suggest that velocity abnormalities occur early in hypertension and may be an appropriate target for preventive strategies because they occur before abnormalities in global e.

**Editor’s Comment:** Novel noninvasive imaging approaches and biomarkers may have an important role for early identification of patients at high risk for development of heart failure. This study suggests that an substantial number of patients with hypertension may have subclinical depression of regional systolic function as assessed by 2-D speckle-strain echocardiography despite the fact that traditional indices of myocardial function such as ejection fraction and fractional shortening may reveal normal systolic function, especially when relative wall thickness is high. These data add to a growing body of evidence that both diastolic dysfunction and regional systolic dysfunction precede global systolic dysfunction. However, outcome studies are needed to prove that these measures are incremental to global systolic function in predicting risk to development of heart failure. If proven and feasible with echocardiography, these measures could be an appropriate target for preventive strategies.

Mechanism of Decrease in Mitral Regurgitation After Cardiac Resynchronization Therapy Optimization of the Force-Balance Relationship

**Summary:** Cardiac resynchronization therapy (CRT) is associated with a reduction in functional mitral regurgitation (MR). However,
the precise mechanism of MR reduction is incompletely defined. Normal mitral valve (MV) function results from a balance of both tethering and left ventricular (LV) closing forces on the MV. Tethering forces, transmitted through the chordae, keep the valve from prolapsing, whereas closing forces depend on the pressure generated by the ventricle to close the MV. Functional MR results from a derangement in this force-balance relationship of tethering and closing forces. There are 2 potential mechanisms by which CRT may reduce MR. One mechanism relates to reverse remodeling effects of CRT on the LV and MV geometry, resulting in improved spatial relationships of the MV to the ventricle and reduction in leaflet tethering. A second mechanism relates to improved LV contraction with an increase in LV pressure generation after CRT and increased closing forces on the MV with improved leaflet coaptation. To better understand the mechanism of MR reduction after CRT, we examined LV and MV geometry, using 3D echocardiography and the transmitial closing pressure pattern using Doppler echocardiography, at baseline and 6 months after CRT. The latter is an integrated measure of LV force generation and reflects the coordinated impact of closing forces on the MV throughout systole. Our results show that MR reduction after CRT is associated with both reduced tethering of the MV through beneficial affects on LV remodeling and increased LV contraction forces on the MV. It has been proposed that the mechanism of MR reduction relates to geometric change or, alternatively, changes in LV contractile function. Normal MV function relies on a balance between tethering and closing forces on the MV leaflets. Functional MR results from a derangement of this force-balance relationship, and CRT may be an important modulator of MV function by its ability to enhance the force-balance relationship on the MV. We hypothesized that CRT improves the comprehensive force balance acting on the valve, including favorable changes in both geometry and LV contractile function.

Conclusions: Reduction in MR after CRT is associated with favorable changes in LV geometry and closing forces on the MV. It does so by favorably affecting the force balance acting on the MV in 2 ways: reducing tethering through reversal of LV remodeling and increasing the systolic duration of peak transmitial closing pressures.

Editor’s Comment: The mechanism of improvement in LV function with CRT remains an ongoing area of investigation. In this study, the authors use 3D echocardiography to focus specifically on the mechanism of improvement in functional MR after CRT. The comprehensive geometric and functional assessment of MV closure demonstrates the complex interplay of changes with CRT that favorably affect the force-balance relationship on the valve. There was no clear association with measures of dysynchrony, and this study further highlights why investigators have struggled to find consistent indices that predict response to CRT.

Comparison of Aortic Root Dimensions and Geometries Before and After Transcatheter Aortic Valve Implantation by 2- and 3-Dimensional Transesophageal Echocardiography and Multislice Computed Tomography

Summary: Current 2D echocardiographic techniques assume circular aortic root geometry when calculating cross-sectional areas. Previous studies have demonstrated that the aortic annulus and left ventricular outflow tract have an ellipsoidal geometry but failed to quantify the extent of underestimation caused by this geometric assumption. This may have important clinical implications for selection of appropriate transcatheter aortic valve sizes, which is currently based on 2D echocardiographic measurements. Furthermore, changes in the aortic root dimensions and geometries after transcatheter aortic valve implantations are unknown. Using multislice computed tomography as the “clinical gold standard,” the present study quantified the degree of aortic root cross-sectional area underestimation caused by the assumption of circular aortic annular and left ventricular outflow tract geometry. Furthermore, we demonstrated that 3D transesophageal echocardiography had the best agreement with multislice computed tomography. Finally, after transcatheter aortic valve implantations, the left ventricular outflow tract and aortic valve annulus became more circular-shaped. The use of 3D imaging may have implications in the calculation of aortic valve area by continuity equation and the selection of appropriate transcatheter aortic valve sizes.

Conclusions: Before transcatheter aortic valve implantation, 2D and 3D transesophageal echocardiography aortic annular/left ventricular outflow tract circular geometric assumption underestimated the respective multislice computed tomography planimetered areas. After transcatheter aortic valve implantation, 3D transesophageal echocardiography and multislice computed tomography planimetered annular areas decreased as it assumes the internal dimensions of the prosthetic valve. However, planimetered left ventricular outflow tract areas increased as the result of a more circular geometry.

Editor’s Comment: There is growing evidence that noninvasive imaging plays an important role in the delineation of vascular access and measurements of left ventricular outflow tract and aortic valve annulus for selecting patients under consideration for transcatheter aortic valve implantation. This study uses cardiac CT as a gold standard to determine the accuracy of 2D with 3D echocardiography to measure ventricular outflow tract and aortic valve annulus before and after transcatheter aortic valve implantation. This small validation study demonstrates that 3D echocardiography may improve the preoperative assessment of patients with large and eccentric outflow tracts and valve areas and the subsequent selection of appropriate transcatheter aortic valve sizes. This study suggests that further studies should focus on the comparison of the effectiveness of cardiac CT versus 3D echocardiography in this clinical application.

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 tomography 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.

Editor’s Comment: Changes in LV contractile function occur after MV surgery, but the relationship to changes in oxidative metabolism is unclear. In this innovative study, the authors use radiolabeled C-11-acetate measured with positron emission tomography to assess oxidative metabolism and calculate an LV performance index noninvasively. It is a small study in patients who had MV surgery and demonstrates that the improvement in LV volume and forward stroke volume do not occur at the expense of oxidative metabolism. This technique may be useful in comparing different types of MV surgery and other innovative approaches to valve surgery.
Echocardiography Can Identify Patients With Increased Pulmonary Vascular Resistance by Assessing Pressure Reflection in the Pulmonary Circulation

Summary: Pulmonary hypertension is a frequent finding in patients investigated with Doppler echocardiography. Most of these patients have left heart disease with pulmonary hypertension secondary to an increase in the left ventricular filling pressure with normal pulmonary vascular resistance. Pulmonary vascular disease with increased resistance to flow leads to pulmonary hypertension with a poor prognosis due to right ventricular failure. Diagnostic delay is a well-known problem in patients with pulmonary hypertension caused by pulmonary vascular disease. It is important to distinguish patients with pulmonary hypertension caused by increased pulmonary vascular resistance from those with pulmonary hypertension caused by increased left ventricular filling pressure without increased resistance, as this affects both treatment and prognosis. Low pulmonary artery mean pressure, low peripheral resistance, and high compliance in the central large arteries characterize the normal pulmonary circulation, and, together, this causes little reflection of the pressure wave. In the present study, we hypothesized that pressure reflection and its effect on the right ventricle pressure profile can be described noninvasively by using Doppler echocardiography. Further, we tested the hypothesis that variables associated with pressure reflection can be used to identify patients with increased pulmonary vascular resistance. We found that Doppler echocardiography can be used to describe pressure reflection in the pulmonary circulation, and, importantly, the method can be used to identify patients with increased pulmonary vascular resistance.

Conclusions: In this study, we describe a novel echocardiography method for assessing pressure reflection in the pulmonary circulation. This method can be used to identify patients with pulmonary hypertension due to increased pulmonary vascular resistance.

Editor's Comment: The assessment of the pulmonary vascular bed is clinically important. Although echocardiography is routinely used to estimate pulmonary artery systolic pressure, methods for determining pulmonary vascular resistance have been limited. In this report, the authors report that 3 variables that are related to pulse wave reflection can be derived from Doppler-derived pulmonary artery and tricuspid regurgitant jet spectra. These parameters, time from pulmonary valve opening to peak pulmonary artery velocity, the interval between pulmonary artery peak velocity and peak tricuspid velocity, and the right ventricular pressure increase after peak velocity in the pulmonary artery (augmented pressure), were validated against invasive determinations of pulmonary vascular resistance. The new parameters were significantly different in patients with pulmonary hypertension. They did not correlate with invasively derived pulmonary capillary wedge pressure. This new measure will complement existing echo-Doppler approaches for assessing pulmonary vascular hemodynamics.

Multimodality Imaging Reveals a Gradual Increase in Matrix Metalloproteinase Activity at Aneurysmal Lesions in Live Fibulin-4 Mice

Summary: Aneurysms can be identified with ultrasound or CT and can be treated by open or endovascular surgery once they have formed. However, the loss of vessel wall integrity that precedes aortic dilatation cannot be detected or treated. In an experimental model, we have identified that deficiency of the fibulin-4 gene encoding the extracellular matrix protein fibulin-4 induces aortic aneurysm formation. Additional protein expression analysis revealed extracellular matrix degradation proteases, such as matrix metalloproteinases, as key biomarkers in aneurysm formation. Using a fluorescence tomographic imaging system, we have been able to monitor the increased protease activity in vivo in our fibulin-4 knockdown mice with protease-activatable, near-infrared fluorescent probes before the aneurysm had actually formed. Implementation of this novel molecular imaging technique in humans will provide a diagnostic tool to predict aneurysm formation in patients. At present, these fluorescence tomographic imaging systems are only suited for experimental research on relatively small-animal models. However, fiberoptic angioscopy is a promising tool for diagnostic imaging of protease activity in the vascular system because the fiberoptic catheter is applicable to humans and does not require large imaging equipment. In addition to conventional imaging modalities, these new diagnostic tools that interrogate the aneurysmatic lesion could potentially serve to test pathophysiological hypotheses to identify the risk while the disease remains undetected and to evaluate novel therapeutic strategies. Future work will answer whether these imaging approaches can further improve our ability to diagnose the disease, assess treatment efficacy, and allow clinical translatability.

Conclusions: We aimed to develop molecular imaging procedures for faster, earlier, and easier recognition of aortic aneurysms. We show that in vivo coregistration of matrix metalloproteinase activity by noninvasive tomographic imaging methods allows the detection of increased matrix metalloproteinase activity, even before the aneurysm has actually formed.

Editor's Comment: Noninvasive measurement of aortic size is the current standard for diagnosis and surveillance of patients with aortic aneurysms. Although this has proven to be very effective, more sensitive tests for identification of patients at risk for complications could prove useful for optimization of the timing of aneurysm repair. This study provides initial validation of a fluorescence tomographic imaging system and reporter imaging probe to monitor the increased matrix metalloproteinase activity in vivo in a mouse model of aortic aneurysm. Future work will answer whether these invasive imaging approaches can further improve our ability to diagnose the disease, assess treatment efficacy, and allow clinical translatability.

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 can 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. Editor’s Comment: The reduction of FMR with dobutamine infusion has been used to predict “viability” of the functionally leaky mitral valve. This study offers insights into why FMR improves by incorporating regional quantitative LV strain analysis to cardiomyopathy patients with FMR and no structural mitral valve abnormality who are undergoing dobutamine stress echocardiography. The predictive value of increase in inferior systolic strain rate for reduction in ERO after multivariable analysis suggests utility for future studies that seek to improve prognosis through therapies that address FMR and its etiologic mechanisms.

Relief of Mitral Leaflet Tethering After 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. After infarction, 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 after 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.

Editor’s Comment: Excess traction on the mitral leaflets exerted through the chordae is an important mechanism of the apical tethering that characterizes ischemic/functional MR. Consequently, chordal cutting has been shown to acutely reduce apical tethering and concomitant MR in an animal model of ischemic MR and in some patients. Whether this intervention also favorably influences LV remodeling has not previously been reported. In this study, an ovine model of ischemic MR, chordal cutting was shown to limit the progressive increases in LV end-diastolic and end-systolic volume that occurred in control (sham-operated) animals and was also associated with a sustained reduction in MR. LV ejection fraction and wall motion score were similar in animals that underwent chordal cutting versus controls. This provides support for the use of chordal cutting as a therapy for some patients with ischemic MR.

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 long-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.

Editor’s Comment: Degenerative MR may coexist with medical indications for β-blockade. Since β-blockers have been shown to increase LV end-diastolic and end-systolic volumes, there is a theoretical possibility that β-blockade might also influence mitral annular geometry and possibly the severity of MR. Somewhat paradoxically, this study reports that whereas β-blockade causes more extensive changes and the impact, if any, of the observed change on the severity of MR would need to be assessed in follow-up studies.

Mitril and Tricuspid Annular Velocities Before and After Pericardiectomy in Patients With Constrictive Pericarditis

Summary: The diagnosis of constrictive pericarditis often is challenging, even after multiple diagnostic tests. Tissue Doppler imaging of the mitral annulus has facilitated the identification of constriction, which potentially is curable by pericardiectomy. Preserved or augmented medial annulus early diastolic velocity in a patient with heart failure and normal ejection fraction points to the diagnosis of constriction. However, this finding is not helpful in young patients who normally have preserved early diastolic mitral annulus velocity. The additional finding of lower mitral lateral annulus early diastolic velocity strongly suggests the diagnosis of constriction, it may be reduced if there is superimposed myocardial disease. Even in this situation, the mitral lateral annulus velocity usually is lower than that at the medial annulus. The fact that annular velocities return to lower values after pericardiectomy confirms that the characteristic annulus velocity pattern observed is a product of constrictive pericardium. We must take advantage of this simple measurement when evaluating a patient with heart failure and normal left ventricular ejection fraction.

Conclusions: The mitral lateral/medial e’ ratio is reversed in three-fourths of patients with constrictive pericarditis. All annular velocities are lower in secondary compared with primary constrictive pericarditis before pericardiectomy. After pericardiectomy, there is reduction of all annular velocities and normalization of the mitral lateral/medial e’ ratio.

Editor’s Comment: Small studies have suggested that hemodynamically significant constrictive pericarditis has the unusual characteristic of increased early diastolic mitral annular velocities (e’) with “paradoxical” higher medial velocities compared with the lateral e’. This larger study confirms the observation and documents the difference between idiopathic constrictive pericarditis and secondary causes. It also shows the improvement in these findings after surgery. Whether these indices can be used to assess the success of surgery or recurrence of disease remains to be assessed.
Pioglitazone Improves Cardiac Function and Alters Myocardial Substrate Metabolism Without Affecting Cardiac Triglyceride Accumulation and High-Energy Phosphate Accumulation in Patients With Well-Controlled Type 2 Diabetes Mellitus

Summary: Cardiac disease is the leading cause of mortality in type 2 diabetes mellitus. The blood glucose–lowering thiazolidinedione pioglitazone has been associated with improved cardiac outcome but also with an elevated risk of congestive heart failure. Use of metformin, at present the drug of choice in the treatment of type 2 diabetes mellitus, showed improved outcome in the United Kingdom Prospective Diabetes Study but has been related to adverse cardiac events in other studies. Using MRI and proton and phosphorus magnetic resonance spectroscopy, as well as [18F]2-fluoro-2-deoxy-d-glucose and [11C]palmitate positron emission tomography, this randomized, controlled, double-blinded study investigated the effects of 24-week treatment with pioglitazone or metformin on myocardial function and metabolism in men with well-controlled, uncomplicated type 2 diabetes mellitus who had no clinical evidence of myocardial ischemia. The major findings revealed that pioglitazone but not metformin improved left ventricular diastolic function and cardiac compliance. In addition, pioglitazone and metformin showed differential action on myocardial substrate metabolism; however, this did not translate into alterations in myocardial high-energy phosphate metabolism or myocardial triglyceride content. Both agents improved whole-body insulin sensitivity. None of the treatments were associated with clinically evident edema or congestive heart failure. These data suggest that for male patients with well controlled, uncomplicated type 2 diabetes mellitus without cardiac ischemia, treatment with pioglitazone may be a good, safe option because it may favorably influence myocardial function.

Conclusions: In type 2 diabetes patients, pioglitazone was associated with improvement in some measures of left ventricular diastolic function, myocardial glucose uptake, and whole-body insulin sensitivity. The functional changes, however, were not associated with myocardial substrate and high-energy phosphate metabolism.

Editor’s Comment: Large, multicenter studies have suggested that aggressive glycemic control not only offers no measurable cardiovascular protection but also may confer excess cardiovascular risk; however, it is not well understood how specific antidiabetic agents affect cardiac function and metabolism to influence this risk. In a randomized, controlled trial of pioglitazone versus metformin in men with type 2 diabetes and no evident cardiovascular disease, van der Meer and colleagues showed that both agents improved glycemic control but that metformin reduced cardiac work whereas pioglitazone improved diastolic function. Lack of association of this improvement with altered myocardial substrate metabolism highlights that gaps remain in our understanding of how to favorably affect abnormalities in myocardial energetics and substrate utilization to reduce cardiovascular risk in diabetes.  

Exercise Pulmonary Hypertension in Asymptomatic Degenerative Mitral Regurgitation

Summary: Current American College of Cardiology/American Heart Association (ACC/AHA) 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 ACC/AHA guidelines state that mitral valve surgery is reasonable in such patients in the presence of exercise PHT (defined as a systolic pulmonary arterial pressure >50 mm Hg) or exercise induced (>60 mm Hg) PHT, this is supported only by level of evidence C (consensus opinion of experts, case studies, or standard-of-care.). This article provides data that support this recommendation by demonstrating that exercise-induced PHT is common, occurring in 46% patients, and is a strong independent predictor of the onset of symptoms. Additionally, the study provides a mechanistic explanation for exercise-induced PHT by noting its relation to the severity of mitral regurgitation during exercise as measured by effective regurgitant orifice area.

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 SPAP >56 mm Hg accurately predicts the occurrence of symptoms.

Editor’s Comment: Although current AHA/ACC guidelines recommend mitral surgery in patients with asymptomatic severe mitral regurgitation and preserved left ventricular systolic function and preserved exercise PHT, this is supported only by level of evidence C. The best cutoff value of exercise 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 rapid development of symptoms. Close follow-up (3–6 months) is advised in asymptomatic patients with 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 appears to be more appropriate in patients without exercise PHT.

Ventricular Geometry, Strain, and Rotational Mechanics in Pulmonary Hypertension

Summary: As a result of ventricular interdependence, analysis of concomitant intrinsic left ventricular (LV) diseases (ie, myocardial fibrosis) in patients with significant pulmonary hypertension (PH) is challenging. The farther a region is from the right ventricle (RV) (eg, the lateral wall), the less the impact will be that the PH has on LV strain. Furthermore, parameters based on circumferential fibers appear to propagate farther from the RV than longitudinal parameters, probably reflecting continuity of the circumferential fibers from the septum to the lateral wall. Accordingly, a finding of abnormal LV lateral wall longitudinal strain in patients with PH might identify true LV dys funcion that is independent of PH. We further demonstrated that LV torsion correlated negatively with estimated pulmonary artery systolic pressure and with septal flattening. Abnormally reduced LV torsion in PH could represent an advanced stage of PH and geometric alteration. Interestingly, although torsion was reduced, untwisting velocity was similar regardless of pulmonary artery systolic pressure. This may reflect the known association of rapid untwisting with reduced LV end-systolic volume, a likely compensatory mechanism to maintain filling in the presence of reduced preload and/or exercise. Further study defining the relationship of LV torsion and untwisting with clinical outcomes and evaluating the effect of PH therapy on LV torsion is needed.

Conclusions: Chronic RV pressure overload directly affects RV longitudinal systolic deformation. RV pressure overload further influences IVS and LV geometry, which impairs LV torsion and segmental longitudinal strain and circumferential strain, more for the interventricular septal than for the free wall of the LV.
Editor's Comment: Ventricular interdependence is well recognized, but the specific effect of RV pressure overload on regional LV mechanics has not been fully elucidated. In this study, the expected impact on the interventricular septum is documented with borderline effect on LV lateral wall strain. However, overall LV torsion is impaired, and whether this manifestation of abnormal LV mechanics contributes to symptoms in these patients will require further study.

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 LV 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 LVOTO 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.

Editor's Comment: It has been known that in patients with hypertrophic cardiomyopathy (HCM), septal thickness does not necessarily correlate with dynamic obstruction, and there is increasing evidence that HCM is more than a myocardial problem. This 3-dimensional echocardiography study changes describe changes in papillary muscle position and mitral leaflet size in HCM. The interaction of these features in the LVOT contributes to functional dynamic obstruction. This anatomic and mechanistic study provides an important foundation for potential individualized strategies to treat HCM.

Myocardial Steatosis and Biventricular Strain and Strain Rate Imaging in Patients With Type 2 Diabetes Mellitus

Summary: The underlying origin of diabetic heart disease is likely to be multifactorial, ranging from altered myocardial metabolism to endothelial dysfunction, microvascular disease, autonomic neuropathy, and altered myocardial structure with fibrosis. Increasing evidence is emerging on the role of lipotoxic myocardial injury from lipid oversupply. Using MRI and proton magnetic resonance spectroscopy, the present study evaluated the association between myocardial triglyceride accumulation and altered biventricular myocardial function by 2-dimensional speckle-tracking echocardiography in type 2 diabetic patients. Diabetic patients with high myocardial triglyceride content had significantly more impaired biventricular myocardial functions despite normal volumes and ejection fraction. On multivariate analyses, myocardial triglyceride content was an independent determinant of biventricular myocardial functions. Future studies assessing the effectiveness of antisteatotic therapy in type 2 diabetic patients may include quantifications of myocardial triglyceride content by spectroscopy and assessments of myocardial functions by strain/strain-rate imaging on 2-dimensional speckle-tracking echocardiography.

Conclusions: High myocardial triglyceride content is associated with more pronounced impairment of left ventricular and right ventricular functions in men with uncomplicated type 2 diabetes mellitus.

Editor’s Comment: Increased heart failure in patients with diabetes beyond the incidence that would be predicted by coronary artery disease and hypertension demands better understanding and preventive strategies. Ng and colleagues offer insights into the potential substrate for excess myocardial disease by demonstrating higher versus lower myocardial triglyceride content in males with uncomplicated type 2 diabetes independently predicted worse left and right ventricular strain. This difference was seen despite similar age, body mass index, glycohemoglobin level, and normal biventricular ejection fractions, suggesting that myocardial steatosis warrants greater consideration as a target for heart failure prevention strategies in diabetes mellitus.

Noninvasive Diagnosis of Electroanatomic Abnormalities in Arrhythmogenic Right Ventricular Cardiomyopathy

Summary: The noninvasive diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC) is based on established criteria. However, the diagnostic reliability and pathophysiologic relevance of different noninvasive findings for the diagnosis of ARVC are undefined because they have never been compared with a diagnostic reference test. In this study, noninvasive diagnostic criteria have been compared with the presence and location of RV myocardial substrate abnormalities assessed as low-voltage areas at 3D electroanatomic voltage mapping in a series of biopsy specimen-proven ARVC. Surface ECG abnormalities were associated with a high degree of RV involvement, whereas late potentials at signal-averaged ECG correlated selectively with low voltages in the RV outflow tract, thus representing a noninvasive marker of myocardial substrate abnormalities of this ventricular segment. Among morphofunctional abnormalities detected at cardiac magnetic resonance, delayed gadolinium enhancement was the finding more strongly associated with the distribution of low-voltage areas. Interestingly, late potentials are included among minor diagnostic criteria, whereas delayed gadolinium enhancement is not yet considered a diagnostic abnormality in ARVC. On the basis of the findings from the present study, an accurate revision of ARVC diagnostic criteria should reconsider the potential role of late potentials at signal-averaged ECG and include delayed enhancement analysis in the noninvasive evaluation of patients with ARVC.

Conclusions: In patients with ARVC, signal-averaged ECG abnormalities correlate with the presence of low-voltage areas selectively in the RV outflow tract, whereas surface ECG abnormalities are associated with a more diffuse RV involvement. Myocardial delayed enhancement is the cardiac magnetic resonance finding more strongly associated with low-voltage areas, thus supporting the appropriateness of its inclusion among diagnostic criteria for ARVC.

Editor’s Comment: Although rare, ARVC is a frequent consideration by electrophysiologists as well as cardiac imaging specialists despite known limitations of clinical and imaging diagnostic criteria. Santangeli and colleagues build on prior work demonstrating correlation
between invasively measured low-voltage areas in RV myocardium and fibrofatty replacement by RV endomyocardial biopsy. In extending this correlation to RV regions of delayed gadolinium enhancement, hypertrophy by cardiac magnetic resonance, this work underscores the critical importance of delayed gadolinium enhancement in evaluation of the patient suspected of having ARVC and offers hope for more reliable cardiac magnetic resonance–based diagnosis.23

References
