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 3.5–4.8-mm hole (HOLE) in the mitral valve posterior leaflet. Nine control sheep were operated on concurrently. At 1 week and 12 weeks after surgery, the 4D motion tracking the motion of radio-opaque markers, was shown to be an undersized annuloplasty ring. 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 mitral regurgitation alone, without the ischemic LV dysfunction that characterizes ischemic MR, negatively affects LV torsion. This adds to our understanding of the pathophysiology of MR.1

Influence of Myocardial Fibrosis on Left Ventricular Diastolic Function Noninvasive Assessment by Cardiac Magnetic Resonance and Echo

Summary: Myocardial fibrosis develops as a final common end point in response to a broad range of cardiac pathologies such as ischemia, inflammation, hypertension, and valvular heart disease. Clinically, these conditions may produce signs and symptoms related to increased myocardial stiffness that may result from replacement or reactive fibrosis. This study used late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) to noninvasively quantify myocardial fibrosis and Doppler echocardiography to detect and classify severity of left ventricular diastolic dysfunction. Regardless of etiology, the presence and severity of diastolic dysfunction increased with the greater extent of myocardial fibrosis. This work suggests that LGE-CMR may be useful to identify the myocardial substrate for impaired relaxation and provides a rationale for its use as an end point in developing novel therapeutics for diastolic dysfunction.

Conclusions: Severity of myocardial fibrosis by LGE significantly correlates with the degree of diastolic dysfunction in a broad range of cardiac conditions. Noninvasive assessment of myocardial fibrosis may provide valuable insights into the pathophysiology of left ventricular diastolic function and therapeutic response.

Editor’s Comment: There has been increased attention directed at the role of the extracellular matrix in heart failure. LGE-CMR has been validated as a reliable marker of interstitial expansion and fibrosis across a wide range of myocardial diseases. Moreo and colleagues performed a retrospective study from a large cardiovascular imaging database comparing echo-Doppler to categorize diastolic function with extent of evident myocardial fibrosis by LGE-CMR. In showing that increased extent of fibrosis predicted worse left ventricular diastolic function, this work supports LGE-CMR as a suitable measure that can be performed serially and noninvasively in therapeutic trials directed at altering the extracellular substrate for diastolic dysfunction in various myocardial diseases. Similar studies using T1 mapping, an emerging technique that may be more sensitive to diffuse interstitial fibrosis, are warranted.2

Left Ventricular Diastolic Function in Type 2 Diabetes Mellitus Prevalence and Association With Myocardial and Vascular Disease

Summary: In the past decade, the term left ventricular (LV) diastolic heart failure or heart failure with normal ejection fraction has been

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introduced. The symptoms of heart failure are believed to be caused by abnormalities in LV filling, which are frequently seen in patients with type 2 diabetes mellitus. Whether LV diastolic dysfunction in patients with type 2 diabetes mellitus is caused by an intrinsic myocardial disorder or related to vascular disease is, however, still controversial. Better understanding of this is imperative for imple-mentation of therapeutic interventions to improve the prognosis of these patients. In the present study, patients with type 2 diabetes mellitus with no history of heart failure or coronary artery disease referred to a diabetes clinic for the first time (n=305) were studied. The present study demonstrated a low prevalence of LV systolic dysfunction (9%); however, the study confirmed a high prevalence of LV diastolic dysfunction (40%). Importantly, the study suggested a close association between the presence of moderate or severe LV diastolic dysfunction and abnormal myocardial perfusion on myo-cardial perfusion scintigraphy, whereas the association with vascular function was considerably less prominent. Thus, the findings support the hypothesis that moderate or severe LV diastolic dysfunction and left atrial dilation in the early phase of type 2 diabetes mellitus are closely associated with intrinsic LV ischemic dysfunction. However, such LV diastolic dysfunction and left atrial dilation are not closely related to vascular disease with arterial stiffening and abnormal ventriculo-arterial coupling.

Conclusions: Abnormal LV filling is closely associated with abnormal myocardial perfusion on myocardial perfusion scintigraphy, whereas the association of LV filling with vascular function is less prominent.

Editor’s Comment: This study confirms the high prevalence of echocardiographically defined diastolic dysfunction in asymptomatic patients with type 2 diabetes. Additionally, it builds the case that myocardial dysfunction caused by subclinical myocardial ischemia is a more important cause of such diastolic dysfunction than vascular dysfunction and resultant abnormal ventriculo-arterial coupling. This study adds to our understanding of the pathophysiology of an important cause of morbidity in type 2 diabetes, an increasingly common condition.

Impact of Loading Condition on the 2D Speckle Tracking–Derived Left Ventricular Dyssynchrony Index in Nonischemic Dilated Cardiomyopathy

Summary: Despite excellent results regarding the use of cardiac resynchronization therapy, a treatment for restoring left ventricular (LV) synchronous contraction in patients with drug-refractory heart failure, approximately 30% of patients do not respond to this sophisticated treatment, underscores the need for better selection criteria. Echocardiographic LV dyssynchrony index has recently been proposed as a better surrogate for predicting positive cardiac resynchronization therapy responders. Heart failure is considered a dynamic condition because LV loading status can be changed by a variety of medications used to improve patient symptoms. To date, however, there are few data concerning the potential influence of LV loading status on the echocardiographic assessment of LV dyssynchrony. The authors investigated the effect of LV loading condition on LV dyssynchrony in patients with nonischemic dilated cardiomyopathy, using speckle-tracking–derived radial strain echocardiography. The measurement of LV dyssynchrony in this study (the maximal difference in time-to-peak radial strain in 2 or 6 segments as well as standard deviation of the time to peak radial strain for 6 segments) were significantly affected by changes in LV loading conditions created by sublingual nitroglycerin administration and pneumatic lower extremity compression. In particular, using 130 ms of difference between the anteroseptal and inferolateral segments as a cutoff value for the presence of LV dyssynchrony, the proportion of patients with LV dyssynchrony significantly changed (29.7% at baseline, 45.9% under pneumatic lower extremity compression, and 35.1% after sublingual nitroglycerin administration). Therefore, LV loading conditions should be considered when echocardiographic assessment of LV dyssynchrony is used for clinical decision-making.

Conclusions: To the best of our knowledge, the present study provides the first evidence of a significant association between LV dyssynchrony and LV loading status, reflective of a dynamic nature of LV dyssynchrony. Accordingly, LV loading conditions should be taken into account when echocardiographic LV dyssynchrony is used for clinical decision-making of selecting candidates for cardiac resynchronization therapy or when it is used as a surrogate marker of prognosis.

Editor’s Comment: Thus far, echocardiography has met its match with the challenge to diagnose LV dyssynchrony. Previous efforts using various echocardiographic indices to determine LV dyssynchrony and predict patient outcomes have failed, indicating the complexity of this condition. This study demonstrates the dynamic nature of LV dyssynchrony during temporary and acute changes in LV loading status. These findings emphasize the importance of standardization of echocardiographic assessment of LV dyssynchrony and the opportunity to derive predictive measures.

Changes in Left and Right Ventricular Mechanics During the Mueller Maneuver in Healthy Adults: A Possible Mechanism for Abnormal Cardiac Function in Patients With Obstructive Sleep Apnea

Summary: Although obstructive sleep apnea (OSA) has been implicated in the genesis of myocardial dysfunction, the mechanisms by which OSA affects myocardial function have not been determined. In this study, the authors focused on the effect of negative intrathoracic pressure, which is a characteristic pathophysiological change in OSA, on cardiac mechanics, using 2D speckle tracking analysis. The Mueller maneuver was performed to simulate OSA in 24 healthy volunteers. During this procedure, a negative intrathoracic pressure of −40 mm Hg was maintained for 12 seconds. The authors measured longitudinal strain and strain rate at baseline, during the Mueller maneuver, and at recovery. The principal findings were that the Mueller maneuver, global longitudinal strain and strain rate in the left ventricle were significantly reduced compared with baseline. These results suggest that negative intrathoracic pressure during apnea may contribute to changes in myocardial mechanics. These findings provide one mechanism through which OSA may be linked to cardiac dysfunction.

Conclusions: Left ventricular and right ventricular longitudinal deformation are significantly reduced during the Mueller maneuver. These results suggest that negative intrathoracic pressure during apnea may contribute to changes in myocardial mechanics. These results could help explain the observed changes in left ventricular and right ventricular mechanics in patients with OSA.

Editor’s Comment: Abnormalities of right and left ventricular function including chronically reduced ejection fraction are well documented in patients with obstructive sleep apnea (OSA). In this study, the authors have reproduced one element of OSA (negative intrathoracic pressure) and have demonstrated that this is associated with acute changes in right and left ventricular strain and, to a more variable degree, right and left ventricular strain rate in normal subjects. Although the changes that occurred here were transient, it is possible that repetitive episodes of OSA and associated negative intrathoracic pressure may over time lead to chronic changes and overt heart failure and thus contribute to the adverse effects of chronic hypoxia and bursts of sympathetic activity that are also considered to be important in the pathophysiology of OSA-associated cardiomyopathy.

Reduced End-Systolic Pressure-Volume Ratio Response to Exercise: A Marker of Subclinical Myocardial Disease in Type 2 Diabetes

Summary: The negative predictive value of exercise stress echocardiography for exclusion of underlying myocardial ischemia in type 2 diabetes mellitus is not well established. Therefore, it represents a target for further investigation.
Emission Tomography Study

Cardiac Magnetic Resonance and Positron

With Dilated Cardiomyopathy: A Tagged

Block Mechanical Derangement in Patients

Metabolic Correlates of Left Bundle-Branch

Myocardial Structural, Perfusion, and

Metabolic Correlates of Left Bundle-Branch

Block Mechanical Derangement in Patients

With Dilated Cardiomyopathy: A Tagged

Cardiac Magnetic Resonance and Positron

Emission Tomography Study

Summary: In patients with dilated cardiomyopathy, the occurrence of left bundle-branch block leads to inhomogeneous left ventricular (LV) activation and deformation. The potentially deleterious consequences on myocardial perfusion, structure, and metabolism have not been well defined; understanding these abnormalities would shed light on the processes by which left bundle-branch block leads to progressive LV dilatation and dysfunction. By means of high temporal resolution tagged cardiac magnetic resonance and positron emission tomography imaging, we demonstrated that the asynchronous LV deformation caused by left bundle-branch block is associated with asymmetrical LV hypertrophy and extensive redistribution of glucose utilization without consistent changes in myocardial blood flow. In particular, the highly coordinated and vigorously contracting lateral region shows hypertrophy and shifts its metabolism to high glucose utilization, nearly exhausting its metabolic reserve. Conversely, the uncoordinated and poorly contracting septum tends to become thinner but with preserved metabolic reserve. The novel pathophysiologic implications of these results pose the basis for future studies of this multi-imaging approach in select dilated cardiomyopathy patients for optimal cardiac resynchronization therapy.

Conclusions: In dilated cardiomyopathy patients, the extensive LV contraction abnormalities induced by left bundle-branch block cause regional myocardial metabolic and structural remodeling, without consistent changes in blood flow.

Editor's Comment: This study demonstrates structural and metabolic remodeling without changes in tissue perfusion in the left ventricle of patients with left bundle-branch block. Specifically, the study shows increased myocardial deformation, thickness, and glucose metabolism in the hypercontractile lateral wall and the opposite changes in the dysynchronous septum. Whether these pathophysiologic changes are central to the remodeling process or predictive of response to resynchronization therapy requires prospective studies.

Early Impairment of Transmural Principal Strains in the Left Ventricular Wall After Short-Term, High-Fat Feeding of Mice Predisposed to Cardiac Steatosis

Summary: Previous magnetic resonance spectroscopy data of elevated myocardial lipids in human subjects with impaired glucose tolerance or type 2 diabetes suggest that lipid overstorage is an early manifestion of type 2 diabetes, preceding heart failure. This study explored the link between short-term dietary, high-fat intake and early changes in left ventricular (LV) wall mechanics in normal and diseased hearts. The approach in studying transgenic mice is the first to combine localized magnetic resonance spectroscopy of cardiac lipid with transmural resolution of 2-dimensional strains in the LV wall, using cardiac tagged MRI at ultrahigh magnetic field (14.1 T). The authors' earlier work showed these strains to change before global impairment of LV function in myopathic hearts. The responses of endocardial and epicardial mechanics, of the in vivo mouse heart, to a 2-week, high-fat diet (HFD) link overstorage of lipid (steatosis) to early impairment in LV wall contractility. The authors report on normal mice and transgenic mice with low levels of cardiac-specific overexpression of the nuclear receptor hormone PPARα (MHC-PPARα) that exhibit elevated myocardial triglyceride. Other strains of MHC-PPARα, with greater expression levels, develop cardiomyopathy and have been reported to mimic the metabolic phenotype of the diabetic heart. The negative consequences of short-term HFD on LV wall mechanics were only apparent in MHC-PPARα hearts and not nontransgenic animals, suggesting an underlying pathophysiological or genetic requirement for cardiac steatosis in the development of early LV dysfunction. The findings contribute new understanding of the risks associated with elevated myocardial lipid for contractile dysfunction preceding cardiomyopathy.

Conclusions: A short-term HFD elevated myocardial lipid measures as determined by magnetic resonance spectroscopy, which became dissociated from TAG content in hearts predisposed to cardiac steatosis. The increased lipid was associated with concurrent, transmural reductions in E1 and E2 strains across the LV wall. Strains were attenuated at the highest levels of lipid accumulation, suggesting a threshold response. Thus, 2-dimensional strains are impaired early and without LV diastolic dysfunction, owing to cardiac steatosis.

Editor's Comment: Abnormalities in diabetes as well as other metabolic syndromes produce myocardial lipid accumulation with poorly understood functional sequelae. In mice engineered to develop myocardial steatosis, Hinkiewicz and colleagues implemented a novel hybrid magnetic resonance protocol combining hydrogen cardiac spectroscopy with tagged cine imaging. In showing that short-term, high-fat feeding impairs myocardial
Relation Between Right Ventricular Function and Increased Right Ventricular \(^{18}\text{F}\)Fluorodeoxyglucose Accumulation in Patients With Heart Failure

**Summary:** Despite significant improvements in the management of heart failure, morbidity and mortality remain high. The comorbid association of right ventricular (RV) dysfunction with left heart failure identifies patients with a particularly poor prognosis. There has been recent clinical interest in the role of metabolic modulation in the treatment of left ventricular dysfunction. An understanding of the metabolic changes in the RV may serve as a potential target for the management of RV failure. This study was designed to characterize myocardial metabolism in the RV of patients with left ventricular failure. RV dysfunction was associated with an increase in RV glucose uptake. This metabolic change was correlated with the severity of RV dysfunction. Larger, prospective studies are required to define the potential clinical implications of this metabolic adaptation.

**Conclusions:** RV dysfunction is associated with an increase in RV FDG uptake, the magnitude of which may be correlated with severity.

**Editor’s Comment:** In patients with systolic heart failure, left ventricular myocardial dysfunction has been associated with a shift from preferential fatty acid oxidation to glucose metabolism. This study shows a similar association in the failing RV. The degree of glucose uptake in the RV was only weakly related to RV afterload and was independent of the etiology of left ventricular dysfunction. The contribution of this unique metabolic phenotype to heart failure progression and prognosis requires further studies.

Noninvasive Estimation of the Rate of Relaxation by the Analysis of Intraventricular Pressure Gradients

**Summary:** Recent studies have shown the limitations of Doppler-derived methods to evaluate ventricular relaxation in the clinical setting. In the present study, the authors propose and validate a new noninvasive index that improves the assessment of left ventricular (LV) relaxation in patients. At end-systole, myocardial relaxation causes flow deceleration and a reversed pressure gradient inside the LV that can be measured using Doppler echocardiography. In an animal model, the authors demonstrate, for the first time, the physiological basis of the Doppler-derived peak reversed ejection intraventricular pressure difference (REIVPD) to assess relaxation and its reliability under a wide range of hemodynamic interventions and loading conditions. A clinical validation study in 50 patients undergoing simultaneous Doppler-echocardiography and high-fidelity LV pressure measurements shows that the new method combined with tissue Doppler mitral annulus velocity (e’) outperforms currently available methods to estimate the rate of relaxation. This new method might be preferred in clinical scenarios where e’ is known to be unreliable, such as mitral valve disease, annular calcification, regional wall motion abnormalities, or conduction disturbances.

**Conclusions:** The Doppler-derived REIVPD provides a sensitive, reliable, reproducible, and relatively load-independent index of the rate of LV relaxation, combined with tissue Doppler measurements of longitudinal function, this method improves noninvasive assessment of LV relaxation in the clinical setting.

**Editor’s Comment:** Assessment of diastolic function continues to be an important goal of noninvasive imaging, and each new technology purports to provide the solution particularly as it relates to load independence. The definition of onset of diastole also varies, and this innovative study looks at the earliest phase of myocardial relaxation, using Doppler-derived peak reversed ejection intraventricular pressure difference combined with tissue Doppler e’. The ability to carefully analyze the different phases of myocardial relaxation and LV filling should promote targeted diagnostic and treatment strategies. The clinical value of these interesting data will need to be tested in a larger cohort of diverse patients.

Late Gadolinium Enhancement Magnetic Resonance Imaging in the Diagnosis and Prognosis of Endomyocardial Fibrosis Patients

**Summary:** It is well established that exercise has a significant benefit on an individual’s health and longevity. The results of this study support the negative impact on right ventricular morphology and function after a prolonged bout of extreme exercise, which appears to influence changes in left ventricular filling. The acute changes are unlikely to require clinical intervention, particularly in view of the previously reported transient nature. That aside, the physiological adaptations identified in this study could help to elucidate the recently observed long-term right ventricular adaptations observed in the ultraendurance athlete. In view of this, there are two key points that the clinician may take from this study: (1) The findings should not influence any advice given to patients regarding the general health benefit of undertaking moderate, regular exercise, and (2) with the ever-increasing participation in extreme ultraendurance exercise, it is important in sports cardiology that the clinician is aware of these acute effects. These points provide greater insight that could influence patient treatment during and after such events, if required.

**Conclusions:** This exploratory study demonstrates right ventricular dilatation and reduction in function after an ultramarathon. Further research is warranted to elucidate the mechanisms responsible for these findings. It is not clear what clinical impact might result from consecutive bouts of postexercise right ventricular dysfunction.

**Editor’s Comment:** This intriguing study employs myocardial speckle tracking in pre and post a 161 km marathon to determine changes in right ventricular and left ventricular function after prolonged exercise. The findings are intriguing because they are likely to represent a transient “cardiac fatigue” process. Although well-trained athletes probably recover from these changes remarkably dominated by diastolic change, they may mimic the natural history of the cardiac fatigue process of untrained people, which takes years or even decades and show them in a flash. Thus, these studies, besides providing potential insights and benefits for training, may also be useful to gain insights into the natural history.

Late Gadolinium Enhancement Magnetic Resonance Imaging in the Diagnosis and Prognosis of Endomyocardial Fibrosis Patients

**Summary:** The authors evaluated the role of late gadolinium enhancement (LGE) cardiovascular magnetic resonance (CMR) for the diagnosis of endomyocardial fibrosis (EMF), using surgical specimens as the standard method. LGE-CMR confirmed the diagnoses of EMF patients on the basis of areas of LGE that were confined to the endocardium as continuous stria from the inflow tract to the apex. Histopathology of fibrous tissue in 14 patients showed typical features of EMF. The study provides evidence that LGE-CMR is a reliable diagnostic tool to confirm EMF.

**Conclusions:** The study provides evidence that LGE-CMR is useful in the diagnosis and prognosis of EMF through quantification of the typical pattern of fibrous tissue deposition.

**Editor’s Comment:** The study of structural myocardial disease, especially the identification of fibrosis, has become an important...
Mitral 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 that helpful in young patients who normally have preserved early diastolic mitral annulus velocity. The additional finding of lower mitral lateral annulus early diastolic velocity compared with the medial annulus increases confidence in the diagnosis of constriction. Although normal or increased mitral medial annulus 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 to 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.

Tissue Doppler Imaging in the Estimation of Intracardiac Filling Pressure in Decompensated Patients With Advanced Systolic Heart Failure

Summary: The ratio of early transmitral velocity to tissue Doppler mitral annular early diastolic velocity (E/Ea) has been correlated with pulmonary capillary wedge pressure in a wide variety of cardiac conditions. However, the reliability of the mitral E/Ea ratio for predicting pulmonary capillary wedge pressure in patients admitted for advanced decompensated heart failure is unknown. A total of 106 prospective, consecutive patients with advanced decompensated heart failure (ejection fraction ≤30%, New Your Heart Association class III to IV symptoms) underwent simultaneous echocardiographic and hemodynamic evaluation on admission and after 48 hours of intensive medical therapy. The authors found the predictive value of baseline mitral E/Ea ratio in estimating pulmonary capillary wedge pressure to be less robust than previously reported, which appears to be related to larger left ventricular dimensions, more impaired cardiac output, and the presence of cardiac resynchronization therapy. In addition, no reliable direct correlation between baseline or changes in mitral E/Ea ratio and pulmonary capillary wedge pressure was found. Taken together, our observations provide an important refinement in the clinical interpretation of the mitral E/Ea ratio as it applies to patient populations in which important confounders such as alterations in myocardial structure, severity of systolic dysfunction, or the presence of synchronized pacing may pose challenges to the accurate prediction of left ventricular filling pressures.

Conclusions: In decompensated patients with advanced systolic heart failure, tissue Doppler–derived mitral E/Ea ratio may not be as reliable in predicting intracardiac filling pressures, particularly in those with larger left ventricular volumes, more impaired cardiac indices, and the presence of cardiac resynchronization therapy.

Editor’s Comment: This study evaluated a single echocardiographic method of assessing pulmonary capillary wedge pressure (E/Ea) and reported that it performed poorly in patients with advanced decompensated heart failure. Because E/Ea is still frequently used in isolation to estimate left ventricular filling pressures, this report serves as a reminder that this simplified approach may be suitable in patients with decompensated heart failure.

Pioglitazone Improves Cardiac Function and Alters Myocardial Substrate Metabolism Without Affecting Cardiac Triglyceride Accumulation and High-Energy Phosphate Metabolism 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 patients with type 2 diabetes mellitus, 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 metformin reduced cardiac work and 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.\(^{15}\)

**Determinants of Left Ventricular Early Diastolic Lengthening Velocity: Independent Contributions From Left Ventricular Relaxation, Restoring Forces, and Lengthening Load**

**Summary:** Measurement of left ventricular early diastolic lengthening velocity (e') by tissue Doppler echocardiography is used clinically to evaluate diastolic function, and the ratio between peak transmitral early diastolic velocity and e' has been introduced as a noninvasive estimate of left ventricular diastolic pressure. A number of studies indicate that e' is closely related to the rate of left ventricular relaxation. The present experimental study indicates that left ventricular transmural pressure at the onset of diastolic filling, which represents a lengthening load (early diastolic load), is another important independent determinant of e'. Clinically, lengthening load would approximate left ventricular end-diastolic pressure. The present study also indicates that restoring forces, analogous to the elastic recoil after release of a compressed spring, is another important independent determinant of e'. Experimentally, restoring forces were quantified as the magnitude of contraction below myocardial resting length. Clinically, this is reflected in end-systolic length and magnitude of contraction. The present study confirmed that rate of relaxation is an independent determinant of e'. In the normal heart, with rapid relaxation, lengthening load and restoring forces are probably the main determinants of early diastolic lengthening velocity. The relative contribution of the different determinants may depend on the functional state of the ventricle, with a more important contribution from rate of relaxation during heart failure.

**Conclusions:** The present study indicates that in the nonfailing ventricle, in addition to left ventricular relaxation, restoring forces and lengthening load are important determinants of early diastolic lengthening velocity.

**Editor’s Comment:** This canine study elegantly explores the determinants of peak early diastolic mitral annular velocity (e', alternatively termed Ea), a parameter that is commonly derived clinically by tissue Doppler imaging. Using the invasively determined time constant of relaxation as a gold standard, the study confirms that relaxation is an important determinant of e' but also demonstrates the importance of early diastolic load and restoring forces. Indeed, the study argues that early diastolic load and restoring forces may be the dominant determinants of e' in the normal heart, with relaxation becoming more important in heart failure. This study is an important contribution to our understanding of noninvasive approaches to assessing diastolic function.\(^{16}\)

**Impact of Myocardial Fibrosis in Patients With Symptomatic Severe Aortic Stenosis**

**Summary:** Aortic valve stenosis remains a diagnostic and therapeutic challenge, particularly in the elderly. In patients with aortic stenosis, left ventricular hypertrophy compensates for pressure overload. Left ventricular hypertrophy may be accompanied by interstitial myocardial fibrosis starting at the subendocardial layers and progressing toward replacement fibrosis. Importantly, fibrosis also may have an impact on patient outcome after aortic valve replacement. In a clinical follow-up study, the authors assessed the degree of myocardial fibrosis and its influence on myocardial function and clinical outcome after aortic valve replacement in patients with symptomatic severe aortic stenosis. The findings support a preoperative diagnostic approach that focuses on the structural abnormalities of the left ventricular myocardium. In this context, myocardial replacement fibrosis appears to be the critical abnormality that can be visualized directly with late-enhancement cardiac MRI in most of these patients. This type of fibrosis has a profound impact on the long-term clinical outcome but remains undetected by standard echocardiographic examination. However, the longitudinal displacement of the mitral ring can be measured reliably during standard echocardiography, captures the functional consequences of myocardial fibrosis, and predicts functional improvement after aortic valve replacement. Thus, the evaluation of mitral ring displacement also may prove valuable for routine preoperative risk assessment.

**Conclusions:** Myocardial fibrosis is an important morphological substrate of postoperative clinical outcome in patients with severe aortic stenosis and was not reversible after aortic valve replacement over the 9 months of follow-up examined in this study. Because markers of longitudinal systolic function appear to indicate sensitively both the severity of myocardial fibrosis and the clinical outcome, they may prove to be valuable for preoperative risk assessment in patients with aortic stenosis.

**Editor’s Comment:** This prospective clinical study evaluated 58 patients with symptomatic aortic stenosis and demonstrated that severity of fibrosis by endomyocardial biopsy correlated with late enhancement by MRI, abnormal left ventricular longitudinal function (as measured by a simple M mode derived displacement of the mitral annulus by echo). Severity of fibrosis was associated with less functional recovery 9 months after aortic valve replacement. This well-designed study provides important pathophysiologic insights into the response of the left ventricle to severe aortic stenosis but, more importantly, provides an easily acquired measurement of longitudinal function that may help predict outcome after aortic valve replacement and perhaps contribute to timing of surgical intervention in asymptomatic patients. This hypothesis will need to be tested.\(^{17}\)

**Age, Increased Left Ventricular Mass, and Lower Regional Myocardial Perfusion Are Related to Greater Extent of Myocardial Dyssynchrony in Asymptomatic Individuals: The Multi-Ethnic Study of Atherosclerosis**

**Summary:** Age and myocardial hypertrophy are associated with the development of left ventricular (LV) dysfunction and heart failure. Myocardial dyssynchrony is also related to the development and progression of heart failure. The goal was to study the relationship of LV mass and age with dyssynchrony in asymptomatic participants of the Multi-Ethnic Study of Atherosclerosis and to obtain more insight into the mechanisms underlying the development of myocardial dysfunction. A total of 1100 individuals underwent tagged MRI. Their regional LV function was analyzed with the use of time parameters of myocardial deformation including time to peak systolic strain and strain rate. Myocardial dyssynchrony was expressed by SD of time to peak strain and strain rate. There was a direct relationship between age and delayed time to peak strain and a greater extent of dyssynchrony. Importantly, there was also significant association between LV mass and time to peak strain, time to peak strain rate, and the SD of time to strain rate. In a subset of patients (n=74), the relationship between myocardial perfusion and timing of contraction was studied. Decreased myocardial perfusion at rest was associated with delayed contraction and increased extent of dyssynchrony. These new data may enhance our understanding of the development of myocardial dysfunction and its possible prevention. The authors believe that myocardial dyssynchrony may explain, at least partly, the well-known association between aging and LV hypertrophy and LV dysfunction. This association may be mediated by changes in myocardial perfusion. However, the temporal relationships between aging, LV hypertrophy, reduced myocardial perfusion, dyssynchrony, and LV dysfunction should be clarified further.
Conclusions: In asymptomatic individuals, age, increased LV mass, and decreased myocardial perfusion are related to delayed myocardial contraction and greater extent of dyssynchrony. Increased dyssynchrony may mediate the association of myocardial dysfunction with age and LV hypertrophy.

Editor’s Comment: This population-based study pioneers advanced imaging technology by using MRI-based myocardial tagging to provide very useful and intuitively correct insights into factors contributing to the development of LV dyssynchrony and its potential role in the development of LV dysfunction. Together with other evidence, the authors confirm the complex nature of the aging of the LV by demonstrating the reduced range for compensation across a variety of vital and complementary LV characteristics such as LV hypertrophy, reduced myocardial perfusion, dyssynchrony, and LV dysfunction.18

Detection of Myocardial Damage in Patients With Sarcoidosis

Summary: In patients with sarcoidosis, sudden death is a leading cause of mortality, which may represent clinically unrecognized cardiac involvement. Delayed-enhancement cardiovascular magnetic resonance (DE-CMR) can detect very small amounts of myocardial damage; therefore, we sought to evaluate the usefulness of DE-CMR for identifying cardiac involvement in 81 consecutive patients with biopsy-proven extracardiac sarcoidosis. When compared with a standard clinical evaluation, which included 12-lead ECG and at least 1 dedicated non-CMR cardiac study (echocardiography, radionuclide scintigraphy, or cardiac catheterization), DE-CMR identified cardiac involvement at a >2-fold higher rate. Patients were also followed up for 21 months on average for major adverse events (death, defibrillator shock, or pacemaker requirement). During follow-up, patients with myocardial damage on DE-CMR had a 9-fold higher rate of adverse events and an 11.5-fold higher rate of cardiac death than patients without damage. On the basis of these findings, the authors believe that DE-CMR is more than twice as sensitive for cardiac involvement as currently used standard methods. Myocardial damage detected by DE-CMR also appears to be associated with future adverse events, including cardiac death, but events were few, and this needs confirmation in a larger cohort.

Conclusions: In patients with sarcoidosis, DE-CMR is more than twice as sensitive for cardiac involvement as current consensus criteria. Myocardial damage detected by DE-CMR appears to be associated with future adverse events including cardiac death, but events were few, and this needs confirmation in a larger cohort.

Editor’s Comment: Patients with extracardiac sarcoidosis are at increased risk for cardiac involvement. Noninvasive diagnosis of cardiac sarcoidosis is challenging, and the conventional right ventricular endomyocardial biopsy has a low sensitivity due to the focal nature of this disease. This study in a relatively large cohort of biopsy-proven extracardiac sarcoidosis demonstrates cardiac involvement, as assessed by the presence of delayed gadolinium enhancement on MRI, in a quarter of patients. In this study, MRI was twice as sensitive as conventional clinical diagnostic criteria. Whether the intensity of late gadolinium enhancement on MRI can be used as a marker of disease activity for guiding treatment will require further studies.19

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 (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 right ventricle 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 dysfunction that is independent of PH. The authors 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, un twisting 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 right ventricular pressure overload directly affects right ventricular longitudinal systolic deformation. Right ventricular pressure overload further influences interventricular septum and LV geometry, which impairs LV torsion and segmental longitudinal strain and circumferential strain, more for the interventricular septum 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 left ventricular mechanics contributes to symptoms in these patients will require further study.20

Equilibrium Contrast Cardiovascular Magnetic Resonance for the Measurement of Diffuse Myocardial Fibrosis: Preliminary Validation in Humans

Summary: Diffuse myocardial fibrosis is a final common end point in cardiovascular disease and is associated with symptoms, impaired ventricular function, and adverse prognosis. Even though it is thought to be a key “missing parameter” in clinical cardiology and it is a target for many therapies (eg, angiotensin-converting enzyme inhibitors, aldosterone antagonists), it can only be quantified by histology on biopsy, with inherent risk and sampling error. As a result, it is not well understood in the clinical arena. Echocardiographic surrogates such as markers of diastolic dysfunction are unsatisfactory because they are influenced by multiple other factors. The authors developed and performed initial validation for a new technique, equilibrium contrast cardiovascular magnetic resonance (EQ-CMR), as a method to quantify diffuse myocardial fibrosis. The authors designed it to be easy to implement on any scanner. EQ-CMR involves standard MRI technology, and contrast agent and can be integrated into a standard CMR protocol. The authors have shown that EQ-CMR correlates with histological fibrosis in 2 conditions, aortic stenosis and hypertrophic cardiomyopathy. This work is at an early stage, but it appears that for the first time, it is possible to measure the diffuse myocardial fibrosis burden noninvasively. With further work, this technique could have widespread implications in disease characterization, monitoring, outcome prediction, and therapeutics.

Conclusions: The authors have developed and validated a new technique, EQ-CMR, to measure diffuse myocardial fibrosis as an add-on to a standard CMR scan, which allows for the noninvasive quantification of the diffuse fibrosis burden in myocardial diseases.

Editor’s Comment: Diffuse myocardial fibrosis occurs in a variety of cardiomyopathies; its reliable detection and measurement have been sought by various noninvasive imaging techniques. Flett and colleagues focus on mapping of the magnetic resonance relaxation parameter T1. In a small group of patients expected to have diffuse fibrosis caused by aortic stenosis or hypertrophic cardiomyopathy, their estimations of myocardial fibrosis obtained preoperatively were...
comparable to direct measurement of collagen volume from intraoperatively sampled myocardium. Further investigations may better delineate the advantages of this approach, which requires a continuous intravenous infusion of gadolinium-based contrast agent, over more typical bolus infusion–based T1 mapping that may not reliably achieve equilibrium of contrast distribution between blood and myocardium.21

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 assessment demonstrating that the mitral leaflet area is increased and that interpapillary muscle distance is shortened and the myocardial 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, 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.22

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.

Editor’s Comment: It has long been recognized that the left ventricular myocardium is not the only determinant of dynamic obstruction in patients with hypertrophic obstructive cardiomyopathy. This 3-dimensional echocardiography study provides a comprehensive assessment demonstrating that the mitral leaflet area is increased and that interpapillary muscle distance is shortened and the interplay contributes to the geometry and functional obstruction of the LVOT. Three-dimensional echo has the ability to elucidate the specific contributors to dynamic obstruction in patients with hypertrophic cardiomyopathy and may provide an approach to tailored therapeutic interventions.22

Relationship of Echocardiographic Dyssynchrony to Long-Term Survival After Cardiac Resynchronization Therapy

Summary: This study demonstrated the association of echocardiographic dyssynchrony with long-term survival after cardiac resynchronization therapy (CRT). The authors studied 229 consecutive patients with routine CRT indications (symptomatic heart failure, reduced ejection fraction, and widened QRS ≥120 ms), of whom 210 (89%) had baseline echocardiographic dyssynchrony data available. Dyssynchrony was prespecified as tissue Doppler longitudinal velocity opposing-wall delay ≥65 ms, 12-site SD (Yu Index) ≥32 ms, speckle tracking radial strain anteroseptal-to-posterior wall delay ≥130 ms, or pulsed Doppler interventricular mechanical delay ≥40 ms. Of 210 patients, there were 62 unfavorable events over 4 years after CRT: 47 deaths, 9 transplantations, and 6 left ventricular assist device implantations. All echocardiographic dyssynchrony indexes were significantly associated with a more favorable long-term prognosis than for patients without dyssynchrony, except tissue Doppler velocity opposing-wall delay became significant at ≥80 ms. When adjusted for covariates of ischemic pathogenesis and QRS width, the Yu Index and speckle tracking radial strain remained independently predictive of outcome. Subgroup analysis demonstrated that patients with narrower QRS width of 120–150 ms who lacked radial dyssynchrony had a particularly poor survival. Although this study has identified the absence of echocardiographic dyssynchrony as a marker for a less favorable prognosis in patients who undergo CRT for routine indications, the potential influence of CRT on outcome in patients without dyssynchrony remains unknown. These observations strongly support the association of echocardiographic dyssynchrony with long-term patient outcome after CRT.

Conclusions: The absence of echocardiographic dyssynchrony was associated with significantly less favorable event-free survival after CRT. Patients with narrower QRS duration who lacked dyssynchrony had the least favorable long-term outcome. These observations support the relationship of dyssynchrony and CRT response.

Editor’s Comment: The utility of echocardiographic indices of dyssynchrony to predict response to resynchronization therapy remains unclear, with divergent data not only around which index is optimal but even whether echo assessment is useful in decision-making. This longitudinal study does not resolve the controversy but in a large group of sick patients from a single center, assesses the utility of various indices to predict long-term survival after CRT. The most useful clinical message is that the lack of echo-determined dyssynchrony is associated with the least favorable event-free survival, particularly if associated with a narrower QRS complex (between 120 and 150 ms).23

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. In multivariate analyses, myocardial triglyceride content was an independent determinant of biventricular myocardial functions. Future studies assessing the effectiveness of antistatic 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
subject for excess myocardial disease by demonstrating higher versus lower myocardial triglyceride content in men with uncomplicated type 2 diabetes independently predicted worse left and right ventricular strain. This difference was seen despite similar age, body mass index, and 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.24

**Echocardiographic Strain Imaging to Assess Early and Late Consequences of Sarcomere Mutations in Hypertrophic Cardiomyopathy**

**Summary:** Hypertrophic cardiomyopathy (HCM) provides a paradigm for using genetic discoveries to better predict and prevent disease. HCM is caused by mutations in sarcomere genes, resulting in left ventricular hypertrophy (LVH) and an increased risk of heart failure and arrhythmias. Genetic testing allows identification of a unique cohort of sarcomere mutation carriers (G+) who have not yet developed traditional phenotypic manifestations of disease (LVH, denoted preclinical HCM). By studying preclinical HCM, early manifestations of sarcomere mutations can be characterized, before pathological cardiac remodeling. To investigate the early and late consequences of sarcomere mutations on cardiac function, echocardiographic strain in preclinical HCM was compared with overt HCM and normal controls. The authors report different patterns of LV contractile abnormalities in early versus late disease. Preclinical HCM is characterized by LV diastolic dysfunction with preserved systolic strain. In contrast, both diastolic and longitudinal LV systolic functions are significantly reduced in overt HCM despite normal LV ejection fraction. They propose that although LV diastolic dysfunction occurs as an early consequence of the underlying sarcomere mutation, systolic dysfunction results from the mutation in combination with the distinctive changes in myocardial architecture that accompany clinical disease. These results have potentially important clinical implications because they raise the possibility that future treatment to diminish the development of myocyte disarray, fibrosis, and hypertrophy, starting in the preclinical stage, may attenuate loss of LV systolic function and retard progression to symptomatic heart failure in HCM, a premise that warrants further study. Identifying mechanistic pathways triggered by sarcomere mutations may begin to reshape paradigms for clinical treatment of HCM, including strategies for early diagnosis and disease prevention.

**Conclusions:** Sarcomere mutations have disparate initial effects on diastolic and systolic functions. Preclinical HCM is characterized by impaired relaxation but preserved systolic strain. In contrast, both diastolic and longitudinal systolic abnormalities are present in overt disease, despite normal ejection fraction. The authors propose that diastolic dysfunction is an early consequence of sarcomere mutations, whereas systolic dysfunction results from mutations combined with subsequent pathological remodeling. Identifying mechanistic pathways triggered by these mutations may begin to reshape the clinical paradigm for treatment, based on early diagnosis and disease prevention.

**Editor's Comment:** Identifying early subtle myocardial abnormalities in patients with preclinical HCM provides the potential to track clinical progression from the earliest manifestation of disease. This study demonstrates somewhat predictable findings from animal models as well as from other myocardial diseases that diastolic dysfunction precedes overt systolic dysfunction, although the use of echocardiographic measurement of systolic strain is a more sophisticated and sensitive measure of systolic dysfunction. This well-designed study builds on the foundation for identifying the mechanistic pathways that result from sarcomere mutations and should help to direct specific treatment early in the disease.25

**Sarcomere Mutations in Cardiomyopathy With Left Ventricular Hypertrabeculation**

**Summary:** Mutations in the gene encoding the sarcomere have been linked to hypertrophic and dilated cardiomyopathy. Recently, mutations in MYH7, ACTC, and TNNT2 have been reported in families and sporadic individuals with left ventricular noncompaction, a disorder in which there is hypertrabeculation of the left ventricle and cardiomyopathy. Normally, during heart development, the left ventricle is transiently heavily trabeculated to allow for oxygenation before formation of the coronary arteries. After vascular development, the inner layer of the left ventricle remodels into the mature compacted appearance. Persistence of deep trabeculae in a postnatal heart is variable, but in its severe form, left ventricular noncompaction can be associated with heart failure and thromboembolic events. The authors implemented clinically available genetic testing in 3 patients with left ventricular noncompaction cardiomyopathy. Two of these individuals were children and 1 was an adult with similarly afflicted family members. The authors found dominant mutations in MYH7 in 2 of the individuals, including the family with adult and pediatric affected members. In the third individual, the authors identified 2 different MYBPC3 mutations carried on different chromosomes, consistent with a complete absence of normal myosin-binding protein C. The myocardium from this individual had an absence of discernable M lines, now implicating cardiac myosin-binding protein C as a potential gene for left ventricular noncompaction. These findings suggest that individuals with hypertrabeculation and cardiomyopathy could be considered for screening for the presence of sarcomere mutations.

**Conclusions:** Genetic testing should be considered for cardiomyopathy with hypertrabeculation.

**Editor's Comment:** Using morphological traits and the phenotype to characterize individuals at risk for the development of certain diseases has long been a major goal of imagers and those who use imaging to make management decisions. This study provides such an example for using a phenotype-genotype correlation to identify individuals at risk. Specifically, they are linking left ventricular hypertrabeculation with sarcomere mutations, thus potentially identifying patients at risk to develop cardiomyopathy.26

**Episodes of Acute Heart Failure Syndrome Are Associated With Increased Levels of Troponin and Extracellular Matrix Markers**

**Summary:** Increased myocyte loss and extracellular matrix (ECM) turnover are central mechanisms that contribute to pathological myocardial remodeling in chronic heart failure (HF). Patients with chronic HF frequently have episodes of acute HF syndromes (AHFS), with interstitial fluid overload, elevated cardiac filling pressures, depressed cardiac output, and the attendant symptoms, with a negative prognostic impact in HF course. Despite the importance of AHFS, little is known about its pathobiology. The major finding of this study is that episodes of AHFS are associated with transient increases in the blood levels of troponin I, a marker for cardiac myocyte injury, and 3 markers for ECM turnover (matrix metalloproteinase [MMP]-2, TIMP-1, and PIIINP). Compared with patients with chronic stable HF, troponin I and these ECM markers were elevated in patients with AHFS. Furthermore, when patients with AHFS returned to chronic stable HF, all of the elevated markers returned to or toward the levels observed in the chronic stable HF group. In contrast, patients with stable HF had only a modest increase of troponin I levels above that in non-HF controls and little or no alteration in any of the ECM markers. An important implication of our observations is that episodes of decompensation may be associated with an acceleration of pathological myocardial remodeling. These observations should stimulate further studies of the pathobiology of AHFS and, ultimately, may have implications regarding the importance of preventing episodes of acute decompensated HF and the identification of therapeutic targets related to cell function.
death and ECM turnover in this setting.

Conclusions: Episodes of AHFS are associated with transient increases in markers of myocyte injury and ECM turnover that may reflect an acceleration of pathological myocardial remodeling during AHFS.

Editor’s Comment: Although acute decompensation of chronic HF has been associated with increased myocardial strain, oxidative stress, and inflammation, the implications of these pathological alterations on myocyte damage have not been studied. This study provides evidence that during AHFS, there is marked increase of plasma troponin I and markers of collagen turnover such as MMPs, tissue inhibitors of MMPs, and other collagen fragments. Most of these markers remain high at discharge despite improved hemodynamic status and come back to background levels a few weeks after returning to compensated HF. The study highlights the importance of preventing episodes of acute decompensated HF and offers possible mechanistic insights into the link between HF decompensation and outcomes.

Ventricular Remodeling and Survival Are More Favorable for Myocarditis Than for Idiopathic Dilated Cardiomyopathy in Childhood: An Outcomes Study From the Pediatric Cardiomyopathy Registry

Summary: A child presenting with a newly diagnosed dilated cardiomyopathy phenotype often has myocarditis that may spontaneously resolve, lead to a chronic dilated cardiomyopathy, or lead to death or heart transplantation. The authors sought to determine the frequency of these divergent outcomes in children diagnosed with myocarditis and to define characteristics at presentation that might be predictive of ultimate outcome using the Pediatric Cardiomyopathy Registry database (PCMR). The analysis resulted in several important findings: (1) The authors noted that most patients diagnosed with myocarditis have normalization of their ventricular size and systolic function over time, often within several months. Normalization is especially likely to occur when patients with diminished systolic function present with a normal left ventricular diastolic diameter or with a greater left ventricular posterior wall thickness. (2) Children who have poorer systolic function at presentation are more likely to die when assessed by multivariable analysis. About one-fourth of patients diagnosed with myocarditis died or were transplanted by 3 years from presentation. (3) There were no significant differences in outcomes in myocarditis patients with and without biopsy confirmation of active myocarditis, using the Dallas criteria. In fact, these 2 groups of patients were remarkably similar to one another in terms of demographics, initial echocardiographic findings, and outcomes. However, these patients had markedly better outcomes than PCMR patients diagnosed with idiopathic dilated cardiomyopathy.

Conclusions: Children with biopsy-confirmed or probable myocarditis had similar proportions of death, transplant, and echocardiographic normalization 3 years after presentation and better outcomes than those of children with idiopathic dilated cardiomyopathy. In children with myocarditis who had impaired left ventricular ejection at presentation, rates of echocardiographic normalization were greater in those without left ventricular dilation and in those with greater septal wall thickness at presentation.

Editor’s Comment: The PCMR is one great demonstration for the usefulness of registries in the research of either rare diseases or specific populations. The data presented are helpful to assess the usefulness of more invasive diagnosis of myocarditis in this vulnerable population.

References


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