A Simultaneous X-Ray/MRI and Noncontact Mapping Study of the Acute Hemodynamic Effect of Left Ventricular Endocardial and Epicardial Cardiac Resynchronization Therapy in Humans

Summary: The absence of clinical response in 30% to 40% of patients receiving cardiac resynchronization therapy (CRT) poses a great challenge to heart failure clinicians and device implanters. It is well documented that positioning of the left ventricular (LV) lead in areas of myocardial scar in patients with ischemic cardiomyopathy is associated with a diminished response to CRT. Regions of slow conduction exist in both nonischemic and ischemic cardiomyopathy that can be delineated using noncontact mapping, whereby the electrophysiological properties of a chamber can be characterized using a multielectrode array. Using this technique, the authors evaluated the effect of pacing inside and outside regions of slow conduction on acute hemodynamic response to CRT. Procedures were performed in a combined x-ray and MRI environment so that tissue characterization by delayed-enhancement cardiac MRI could be correlated with electrophysiological assessment. Both endocardial and transvenous epicardial LV pacing were performed with the hypothesis that endocardial pacing may be more effective as a result of reproducing the physiological pattern of activation of the LV myocardium as well as a lack of constraint by the coronary venous anatomy. The authors found that zones of slow conduction could be identified using delayed-enhancement cardiovascular magnetic resonance in patients with an ischemic heart failure etiology but not in patients with nonischemic cardiomyopathy. The short-term effect of CRT was superior in response to endocardial compared with epicardial pacing. Stimulation within zones of slow conduction was associated with a diminished response to CRT. This is a potential explanation for the absence of clinical response in patients without ischemia.1

Conclusions: Endocardial LV pacing appears superior to conventional CRT, although the optimal site varies among patients and is influenced by pacing within areas of slow conduction. Delayed-enhancement cardiovascular magnetic resonance was a poor predictor of zones of slow conduction in patients without ischemia.1

Relative Merits of Left Ventricular Dyssynchrony, Left Ventricular Lead Position, and Myocardial Scar to Predict Long-Term Survival of Ischemic Heart Failure Patients Undergoing Cardiac Resynchronization Therapy

Summary: The present study demonstrated the relative merits of left ventricular (LV) dyssynchrony, LV lead position, and myocardial scar to predict long-term outcome of patients with ischemic heart failure treated with cardiac resynchronization therapy. With speckle-tracking radial strain analysis, the extent of LV dyssynchrony, site of latest mechanical activation, and presence of myocardial scar at the LV segment where the LV pacing lead was placed were evaluated. In addition, the LV lead position was derived from chest radiograph and was defined as concordant when the LV pacing lead coincided with the site of latest mechanical activation. Mean baseline LV radial dyssynchrony was 133 ± 98 ms. A concordant LV lead position was reported in 271 (68%) patients, and the mean value of peak radial strain at the targeted segment was 18.9 ± 12.6%. During a median follow-up of 21 months, 88 (22%) patients died. Larger LV radial dyssynchrony at baseline was an independent predictor of superior long-term survival (hazard ratio, 0.995 per 1-ms increment; P = 0.001), whereas a discordant LV lead position (hazard ratio, 2.086; P = 0.001) and myocardial scar in the segment targeted by the LV lead (hazard ratio, 2.913; P < 0.001) were independent predictors of worse outcome. Addition of these 3 parameters yielded incremental prognostic value over the combination of clinical parameters. These data underscore the need for integrated evaluation that includes assessment of these 3 parameters to further improve patient selection and survival after cardiac resynchronization therapy.

Conclusions: Baseline LV radial dyssynchrony, discordant LV lead position, and myocardial scar in the region of the LV pacing lead were independent determinants of long-term prognosis in patients with ischemic heart failure treated with cardiac resynchronization therapy. Larger baseline LV dyssynchrony predicted superior long-term survival, whereas discordant LV lead position and myocardial scar predicted worse outcome.2

Prediction of Cardiac Resynchronization Therapy Response: Value of Calibrated Integrated Backscatter Imaging

Summary: According to current guidelines, candidates for cardiac resynchronization therapy (CRT) are patients in New York Heart Association functional class III to IV heart failure with left ventricular (LV) ejection fraction ≤35% and QRS duration ≥120 ms. However, by applying these selection criteria, more than one third of the patients do not show clinical response or LV reverse remodeling. Among several factors that determine a favorable response to CRT, the amount of LV fibrosis as assessed, for example, with cardiovascular magnetic resonance has been shown to be an important issue. This study demonstrated that myocardial ultrasound reflectivity is an important determinant of CRT response in the overall heart failure
population, together with the presence of LV mechanical dyssynchrony and renal function. Moreover, in the ischemic subgroup of patients with heart failure, myocardial ultrasound reflectivity was found to be the only independent determinant of LV reverse remodeling after CRT. In the nonischemic subgroup of patients with heart failure, myocardial ultrasound reflectivity was still an independent predictor of CRT response. Several pathophysiological issues must be addressed to optimize selection of patients for CRT. Different imaging modalities provide information about dyssynchrony, and echocardiography has provided useful, albeit controversial, data in these patients. Myocardial ultrasound reflectivity with calibrated integrated backscatter imaging may provide additional data to aid in the selection of candidates for CRT.

Conclusions: Assessment of myocardial ultrasound reflectivity is important in the prediction of CRT response in patients with and without ischemia.

Dysynchrony, Contractile Function, and Response to Cardiac Resynchronization Therapy

Summary: Although cardiac resynchronization therapy (CRT) has been shown to reduce cardiovascular outcomes in patients with heart failure and left ventricular dysfunction, almost one third of patients who receive CRT do not respond to treatment. Determining which patients are more or less likely to benefit from CRT remains a therapeutic challenge. Left ventricular mechanical dyssynchrony has been suggested as a method for overcoming the limitations of estimating electric dyssynchrony. Echocardiographic assessments of both left ventricular mechanical dyssynchrony and discrete contractile function, which can reflect the extent of myocardial viability and scar burden, now can be performed in a highly reproducible and angle-independent manner by using speckle-tracking analysis. Therefore, in a sample of 1077 patients enrolled in the Multicenter Automatic Defibrillator Implantation Trial-CARDiac Resynchronization Therapy Trial, the authors used echocardiographic myocardial deformation analyses to investigate whether mechanical synchrony and contractility might predict response to CRT. The authors observed that the combination of mechanical dyssynchrony and preserved contractile function significantly predicted lower risk for recurrent heart failure or death after CRT, even after adjusting for factors conventionally associated with CRT response. The results indicated that the ventricle must be not only dyssynchronous, but also viable, as reflected by contractile function, to benefit from CRT. These findings suggest that mechanical dyssynchrony and contractile function are more directly related to clinical response and outcomes than conventionally measured electric dyssynchrony. The analyses were strengthened by the availability of a large sample size, data on long-term clinical outcomes, and the presence of a control group that allowed estimation of the treatment effect.

Conclusions: Both mechanical dyssynchrony and contractile function are important independent correlates of benefit from CRT.

Editor’s Comment: It is well documented that although CRT improves outcomes in patients with advanced heart failure, approximately one third of patients undergoing CRT are nonresponders. Current research efforts are focused on refining selection criteria for maximal clinical benefit. The articles summarized to this point1–4 highlight the potential benefits of tissue characterization and quantification of degree of mechanical dyssynchrony on improving prediction of response to CRT and subsequent outcomes using noninvasive imaging techniques that include ultrasound and MRI. The data suggest that accurate mapping of areas of myocardial scar and careful delineation of the site of latest mechanical activation can be very useful in guiding the placement of pacing leads and translate in improved clinical outcomes.

Cardiac Sympathetic Reserve and Response to Cardiac Resynchronization Therapy

Summary: Heart failure is associated with dysregulated autonomic function with abnormally activated sympathetic and altered parasympathetic tone. This study reported a novel finding that cardiac resynchronization therapy (CRT) modulates sympathetic function, concomitant with its beneficial clinical outcome in patients with drug-refractory heart failure. Electrically and mechanically resynchronized biventricular contractility by CRT upregulates presynaptic receptor function, as evidenced by increased I-123 metaiodobenzylguanidine (MIBG) heart/mediastinum ratio and attenuated heart/mediastinum washout rate, determined by I-123 MIBG scintigraphy, with concurrently improved heart rate variability. The reversal of neuronal remodeling in response to CRT is beyond that achieved by medical therapy, given that all patients have been treated with optimal medications for heart failure. Patients with a less-impaired presynaptic adrenergic preservation (or a better sympathetic reserve) are associated with a greater response to CRT. In perspective, reversible sympathetic inhibition determined by I-123 MIBG may be an imaging marker of clinical response to CRT.

Conclusions: CRT improved sympathetic function. Cardiac sympathetic reserve may be a marker for the reversibility of failing myocardial function.

Evaluation of Left Ventricular Dyssynchrony by Onset of Active Myocardial Force Generation: A Novel Method That Differentiates Between Electrical and Mechanical Etiologies

Summary: Better methods for selection of patients for cardiac resynchronization therapy are required because 30% of patients do not have improved function based on the current QRS duration criterion. Echocardiographic ejection phase indices have previously been introduced without being able to aid in patient selection. In this animal study, the authors introduced a novel method to evaluate dyssynchrony based on assessment of regional onset of active force generation (AFG), that is, the first mechanical sign of actin-myosin interaction. The investigation showed a consistent correspondence between timing of AFG and regional electric activation, indicating that AFG mirrors regional electric activation. In contrast to QRS duration, which is a measure of the total right ventricular and left ventricular (LV) activation time, regional AFG may serve as a better measure of the direct electric activation delay between the LV segments. A patient with synchronous LV activation would be less likely to respond to cardiac resynchronization therapy compared with a patient with long activation delay; hence, this information may complement QRS duration. In this study, the authors showed that ejection phase echocardiographic dyssynchrony indices depend on regional contractile state (ischemia) and load as well as on electric activation delay. Thus, they failed to correctly identify the cause of dyssynchrony, which is important because cardiac resynchronization therapy is designed to correct electric dyssynchrony. On the other hand, AFG correctly reflected electric activation time and did not depend on load or contractile state. The current limitations of the proposed AFG method are that it requires measurements of LV pressure and segment length. In the present study, the authors showed that segment length may be substituted with segmental strain, which can be obtained by echocardiography. This method
Hemodynamic Improvement in Cardiac Resynchronization Does Not Require Improvement in Left Ventricular Rotation Mechanics: Three-Dimensional Tagged MRI Analysis

Summary: Left ventricular (LV) rotation mechanics provide important indices of cardiac function. Earlier studies have yielded conflicting evidence on whether cardiac resynchronization therapy (CRT) improves LV rotation mechanics. This discrepancy may arise from technical and interpretative limitations of the 2D echocardiography that was used in those studies. In the present study, the authors examined the acute effects of CRT on LV rotation mechanics by 3D tagged MRI in dogs with left bundle branch block and tachycardia-induced cardiomyopathy. Three-dimensional tagged MRI is the gold standard technique to measure myocardial motion in vivo, and it allows objective and extensive mapping of the 3D myocardial strain. The results indicated that CRT acutely improves hemodynamic parameters without improving LV rotation mechanics, suggesting that improvement in LV rotation mechanics is specific, but insensitive index of an acute hemodynamic response to CRT.

Conclusions: CRT acutely improves hemodynamic parameters without improving LV rotation mechanics. There is no significant circumferential regional heterogeneity of LV rotation mechanics in the mechanically dyssynchronous heart. The results suggest that LV rotation mechanics is an index of global LV function, which requires coordination of all regions of the LV, and improvement in LV rotation mechanics appears to be a specific, but insensitive index of acute hemodynamic response to CRT.

Editor’s Comment: This study provided a detailed analysis of LV rotation mechanics and its role in the changes in regional and global LV function induced by CRT. Compared with the normal heart, the dyssynchronous ventricle displays a loss of normal twisting and untwisting, which is restored only partially by CRT. Despite this partial restoration of normal rotational mechanics, there is a significant acute improvement in hemodynamics after CRT. This suggests that although specific, LV rotational mechanics is a rather insensitive measure of functional improvement after CRT.

Quantification of Ventricular Resynchronization Reserve by Radionuclide Phase Analysis in Heart Failure Patients: A Prospective Long-Term Study

Summary: The criteria for selecting patients with heart failure for cardiac resynchronization therapy (CRT), namely ejection fraction, New York Heart Association functional class, and QRS width, have been validated in large-scale randomized studies. However, the identification of the precise determinants of the resynchronization reserve, that is, the extent and the origin of the response to biventricular pacing, is lacking. Phase analysis, developed to assess dyssynchrony from ECG-gated radionuclide ventriculography, has shown promising results. The authors hypothesized that quantifying the cardiac resynchronization reserve (ie, the extent of response to CRT) by radionuclide imaging could potentially identify patients who are best suited for CRT. ECG-gated radionuclide ventriculography was performed in 86 patients at baseline with and without CRT and again after 3 months of follow-up. Receiver operating characteristic curve analysis demonstrated that an optimal cutoff value of 25° for interventricular dyssynchrony (IVD) yielded 91.4% sensitivity and 84.4% specificity in predicting a good response to CRT. It was also found that neurohormonal activation was diminished in the group with no clinical events and that when the left ventricular ejection fraction improved, hypokinetic or even dyskinetic segments recovered normal contractility. This improvement continued after 3 months, in agreement with the beneficial anatomic remodeling induced by CRT. Radionuclide ventriculographic phase may offer advantages compared with echocardiographic variables and single-photon emission CT-based phase measurements in selecting patients for CRT. IVD is likely an important predictor of response to CRT. The threshold for IVD determined by receiver operating characteristic curve analysis in this study requires prospective evaluation before generalized use in a heart failure population.

Conclusions: The quantification of IVD with radionuclide phase analysis suggests that early postimplantation IVD may provide identification of CRT responders.

Editor’s Comment: This study evaluated the utility of phase analysis radionuclide ventriculography in determining the response to biventricular pacing in patients with New York Heart Association functional class III and IV congestive heart failure and wide QRS complexes (mean QRS width, 173±25 ms). The early postimplantation IVD and intraventricular dyssynchrony quantitative response was associated with improved outcome and appeared to persist beyond the early 3-month evaluation. The study has provided promising early data, but the experience with numerous echocardiography-derived dyssynchrony parameters, which showed early promise but ultimately were not predictive, should be used as a warning to validate these findings in a larger multicenter cohort.

A Prospective Pilot Study To Evaluate the Relationship Between Acute Change in Left Ventricular Synchrony After Cardiac Resynchronization Therapy and Patient Outcome Using a Single-Injection Gated SPECT Protocol

Summary: There are ongoing efforts to optimize the selection of patients with heart failure for cardiac resynchronization therapy. The authors applied phase analysis of gated single-photon emission CT (SPECT) using a novel single-injection protocol to prospectively measure left ventricular (LV) synchrony before and immediately after clinically indicated biventricular pacemaker implantation. Patients with acutely deteriorated LV synchrony had worse outcome, which was defined as a composite of cardiac death, heart failure hospitalization, appropriate implantable cardioverter-defibrillator discharge, and deactivation of biventricular pacing for worsening symptoms. Furthermore, the acute response to cardiac resynchronization therapy was accurately predicted using baseline gated SPECT-derived information on the presence of LV dyssynchrony, global and regional LV scar, and LV lead concordance with delayed mechanical activation.

Conclusions: In this single-center pilot study, phase analysis of gated SPECT was successfully used to predict acute change in LV synchrony and patient outcome after cardiac resynchronization therapy.
Mechanisms of Abnormal Systolic Motion of the Interventricular Septum During Left Bundle-Branch Block

Summary: In a majority of patients with left bundle branch block, there is abnormal leftward motion of the interventricular septum during isovolumic contraction, often referred to as septal beaking and septal flash when applying M-mode echocardiography and tissue Doppler imaging, respectively. It has not been definitely determined whether this abnormal motion is due to active septal contraction or whether it is represents passive motion caused by an early rise in right ventricular pressure that pushes the septum leftward. The recent interest in quantification of dysynchrony in patients who are candidates for cardiac resynchronization therapy has highlighted the importance of this distinction: If pre-ejection septal motion is due to active contraction, it reflects timing of septal activation and should be included in left ventricular (LV) dysynchrony assessment. If the motion is passive, however, it should not be used for timing of septal activation. The aim of this study was to differentiate between these mechanisms. In an animal model of left bundle branch block, myocardial shortening was measured by sonomicrometry, electric propagation by implanted myocardial electrodes, and right ventricular and LV pressures by micromanometers. The report concluded that the abnormal septal motion during pre-ejection is a result of active septal contraction or whether it is represents passive motion caused by an early rise in right ventricular pressure that pushes the septum leftward. The recent interest in quantification of dysynchrony in patients who are candidates for cardiac resynchronization therapy has highlighted the importance of this distinction: If pre-ejection septal motion is due to active contraction, it reflects timing of septal activation and should be included in left ventricular (LV) dysynchrony assessment. If the motion is passive, however, it should not be used for timing of septal activation. The aim of this study was to differentiate between these mechanisms. In an animal model of left bundle branch block, myocardial shortening was measured by sonomicrometry, electric propagation by implanted myocardial electrodes, and right ventricular and LV pressures by micromanometers. The report concluded that the abnormal septal motion during pre-ejection is a result of active septal contraction or whether it is represents passive motion caused by an early rise in right ventricular pressure that pushes the septum leftward. The recent interest in quantification of dysynchrony in patients who are candidates for cardiac resynchronization therapy has highlighted the importance of this distinction: If pre-ejection septal motion is due to active contraction, it reflects timing of septal activation and should be included in left ventricular (LV) dysynchrony assessment. If the motion is passive, however, it should not be used for timing of septal activation.
Conclusions: In patients with HCM, presence of LGE on contrast-enhanced MRI was common and more prevalent among patients with gene-positive results. LGE was not associated with severe symptoms. However, LGE was strongly associated with surrogates of arrhythmia and remained a significant associate of subsequent SCD and implantable cardioverter-defibrillator discharge after controlling for other variables. If replicated, LGE may be considered an important risk factor for sudden death in patients with HCM.

Editor's Comment: The clinical manifestations of HCM vary, and predicting outcome remains challenging. In a number of areas, LGE has been predictive of adverse outcome. In HCM, LGE is believed to represent intramyocardial fibrosis and, thus, may be useful to predict outcome. In this large retrospective study, the authors addressed this belief and found that LGE is associated with a higher frequency of patients being gene positive for mutations in 9 myofilament-encoding HCM-susceptibility genes, more nonsustained ventricular tachycardia, and subsequent SCD and implantable cardioverter-defibrillator discharge. This retrospective study has built an important foundation for future prospective studies of LGE in HCM to refine features predictive of adverse outcome and to develop approaches to modify treatment in this potentially high-risk group.12

On T2* Magnetic Resonance and Cardiac Iron

Summary: Measurement of myocardial iron is key to the clinical management of patients at risk of iron-overload cardiomyopathy, which is a major killer in transfusion-dependent patients and others with errors of iron metabolism. This applies especially to the large cohort of patients with β-thalassemia major in whom iron accumulation leads to damage in the liver, heart, and endocrine organs. Myocardial iron is assessed clinically with the cardiovascular magnetic resonance (CMR) relaxation parameter T2*. This study described the calibration of CMR relaxation against human iron concentration and the iron distribution throughout the heart under conditions of iron overload. A strong correlation was observed between CMR relaxation measurements and biochemically derived tissue iron concentration in 12 postmortem human hearts from transfusion-dependent patients, leading to the following clinical calibration equation: [Fe] = 45.0 × (T2*)^−1.22, where [Fe] is measured in mg/g dry weight, and T2* is measured in ms. There was no systematic variation in iron concentration throughout the heart, but higher iron levels were found in the epicardium than in the endocardium. The data also showed that CMR measurements in the midventricular septum are very representative of whole-heart iron concentration, which validates the current clinical approach in widespread use. These data show that T2* CMR can be used to measure myocardial iron and validate its use as an end point in clinical trials for the improvement of efficacy of cardiac iron chelation treatment to prevent heart failure and death. This will significantly affect the health care of the many thousands of patients worldwide who depend on transfusion.

Conclusions: These data detail the iron distribution throughout the heart in iron-overload cardiomyopathy, as a Gatekeeper to Invasive Coronary Angiography in Patients Presenting With Heart Failure of Unknown Etiology

Summary: Identifying the underlying etiology in patients with new-onset heart failure and no overt features of underlying coronary artery disease (eg, angina) can be challenging. Invasive coronary angiography (CA) carries tangible risks and does not provide tissue characterization. In this prospective study of 120 patients (powered to display noninferiority), late gadolinium enhancement cardiovascular magnetic resonance (LGE-CMR) showed equivalence to CA when determined against a gold standard consensus panel who considered data from all the investigations. Diagnoses based on LGE-CMR and CA were also validated against clinical outcomes at a median of 3.7 years. LGE-CMR is ideally placed as a gatekeeper to CA because it is safer, uniquely provides biventricular function
and tissue characterization data, and is economically viable. LGE-CMR and CA were equivalent in diagnostic accuracy (97% versus 95%, respectively), and the data suggested that 73% of patients would have appropriately avoided CA, being spared the risks and costs of this investigation. Importantly, no patient with prognostically important coronary artery disease would have been denied CA and any subsequent revascularization because LGE-CMR had a negative predictive value of 100%. The data also suggest the need for a paradigm shift in the classification of patients with heart failure to reflect not only coronary anatomy, but also myocardial tissue characterization. This study, therefore, challenges the traditional dichotomy of ischemic versus nonischemic cardiomyopathy by revealing subgroups of patients with features of both ischemic and nonischemic etiologies.

Conclusions: This study showed that LGE-CMR is a safe, clinically effective, and potentially economical gatekeeper to CA in patients presenting with heart failure of uncertain etiology.

Editor’s Comment: This study evaluated the potential role of cardiac MRI in screening patients with newly diagnosed heart failure for underlying coronary disease. The results that MRI is highly sensitive, specific, and cost-effective relative to a CA approach are interesting, particularly in an era of scrutiny of the use of noninvasive and invasive imaging. However, it should be noted that the cost analysis was based on costs of £600 for MRI and £1255 for CA, and thus, as noted by the authors, may not be valid in settings with different relative costs.15

Cardiac Magnetic Resonance Imaging Pericardial Late Gadolinium Enhancement and Elevated Inflammatory Markers Can Predict the Reversibility of Constrictive Pericarditis After Antiinflammatory Medical Therapy: A Pilot Study

Summary: Constrictive pericarditis (CP) is a disabling disease and usually requires pericardiectomy to relieve heart failure symptoms. Reversible cases of CP after antiinflammatory therapy have been described, but there is no known method to predict the reversibility. This pilot study assessed whether cardiovascular magnetic resonance (CMR) pericardial late gadolinium enhancement (LGE) can predict the reversibility of CP after a course of antiinflammatory therapy. Twenty-nine patients received antiinflammatory medications after CMR. Fourteen had resolution of CP, whereas 15 had persistent constrictive physiology. Baseline LGE pericardial thickness was greater in the reversible CP group than in the persistent CP group. Qualitatively rated severity of pericardial LGE was moderate or severe in 93% of the reversible CP group versus 33% of the persistent CP group. CMR LGE pericardial thickness ≥3 mm had 86% sensitivity and 80% specificity to predict reversibility. The reversible CP group also had a higher baseline C-reactive protein level and erythrocyte sedimentation rate than the persistent CP group. Antiinflammatory therapy was associated with a reduction in pericardial LGE, C-reactive protein level, and erythrocyte sedimentation rate in the reversible CP group but not in the persistent CP group. The findings in this pilot observation suggest that reversible CP is associated with pericardial and systemic inflammation. Furthermore, antiinflammatory therapy is associated with a reduction of pericardial and systemic inflammation as well as pericardial thickness on CMR imaging, with resolution of constrictive physiology and symptoms. Antiinflammatory therapy should be considered in patients with CP with these features before pericardiectomy. The findings need to be validated by further studies in a larger number of patients.

Conclusions: Reversible CP was associated with pericardial and systemic inflammation. Antiinflammatory therapy was associated with a reduction in pericardial and systemic inflammation and LGE pericardial thickness, with resolution of CP physiology and symptoms. Further studies in a larger number of patients are needed.

Editor’s Comment: The treatment of symptomatic CP is clinically challenging, with surgical pericardiectomy the mainstay. However, pericardiectomy may offer incomplete relief, and alternative or complementary medical approaches would be welcomed. In this small study, the authors proposed that pericardial LGE seen with MRI combined with elevated C-reactive protein level and erythrocyte sedimentation rate identify patients with active inflammation who are more likely to respond to antiinflammatory therapy. These encouraging results await confirmation in larger trials, ideally multicenter. Additionally, it will be clinically important to determine whether patients thus identified are rare or constitute a significant proportion of patients with CP.16

Anatomic Localization and Autonomic Modulation of Atrioventricular Junctional Rhythm in Failing Human Hearts

Summary: Since Tawara’s discovery of the atrioventricular node (AVN) in 1906, the AVN has been extensively studied in numerous animal models, using increasingly sophisticated electrophysiological tools. Mapping of the AVN in animals has revealed a number of clinically relevant phenomena, including discontinuous conduction curves, dual pathway AV conduction, and autonomic modulation of the AV junctional pacemaker site. However, until recently, it has been impossible to apply some of the most-sophisticated experimental mapping techniques to the human heart. In 2010, the authors reported the first optical mapping of the human sinoatrial node, which revealed multiple sinoatrial exit pathways connecting the sinoatrial node with the atrial myocardium. The authors presented optical mapping of the human AVN, which revealed patterns of activation long hypothesized but not proven to exist in the human heart. First, the authors presented evidence of fast and slow pathway AVN conduction. Second, they provided evidence of autonomic modulation of the AVN pacemaker. Third, they presented evidence of longitudinal dissociation during AV junctional rhythm, indicating the existence of a functional barrier between the 2 compartments in the human AVN and its extensions, which the authors described in an earlier study. These 2 compartments, the connexin43-negative and connexin43-positive compartments, provide the anatomic and molecular substrate for the fast and slow pathways, respectively. This report provides a functional basis for future molecular and cellular physiology studies in the human AVN, which will be conducted using explanted human hearts. The authors also have opened a possibility for future application of optical mapping in the clinical electrophysiology laboratory.

Conclusions: This study demonstrated that the AV junction pacemaker in failing human hearts is located in the nodal-His region or His bundle regions and can be modified with autonomic stimulation. Moreover, the authors found that both the fast and slow pathways are involved in anterograde and retrograde conduction.

Editor’s Comment: This study investigated pacemaker activity, conduction, and autonomic modulation of the AV junction of failing human hearts, explored at the time of transplantation, using high-resolution optical mapping with correlation of function to the underlying anatomic structures as defined by histology. Importantly, the study confirmed the presence of previously hypothesized patterns of activation as well as evidence of autonomic modulation of the AVN pacemaker. Although the immediate impact of these findings will largely be in the research laboratory, optical mapping has the potential for future use in the clinical electrophysiology laboratory.17

A 4-Tiered Classification of Left Ventricular Hypertrophy Based on Left Ventricular Geometry: The Dallas Heart Study

Summary: Left ventricular hypertrophy (LVH), defined as increased indexed LV mass, is presently classified based on the ratio of the LV
wall thickness to chamber dimension. If this ratio is increased, then the LVH is concentric; otherwise, the LVH is eccentric. The authors proposed a 4-tiered classification based on whether LV concentricity0.67 (LV mass/LV end-diastolic volume0.67 [EDV]) and LVEDV/body surface area are increased. Among 2803 subjects who underwent cardiac MRI, 895 had LVH. Of these, 361 had increased concentricity0.67 but not LVEDV (thick hypertrophy), 53 had increased LVEDV but not concentricity0.67 (dilated hypertrophy), 13 had both increased concentricity0.67 and LVEDV (both thick and dilated hypertrophy), and 468 had neither increased concentricity0.67 nor LVEDV (indeterminate hypertrophy). Subjects with both thick and dilated hypertrophy had a lower LV ejection fraction and higher natriuretic peptide levels versus those with isolated thick hypertrophy. Subjects with indeterminate hypertrophy had a higher LV ejection fraction and lower troponin T and natriuretic peptide levels versus those with dilated hypertrophy and no increase in troponin T or natriuretic peptide levels versus those without LVH. The authors concluded that concentric and eccentric LVH can each be subclassified into 2 distinct subgroups based on the presence of LV dilatation. These data have led to questions about whether LVH should be considered present only if there is increased LV mass, increased LV wall thickness, and ventricular dilation. Refinement of the phenotypic characterization of LVH may improve our understanding of its natural history and provide an opportunity for more-specific and possibly earlier therapeutic intervention.

**Conclusions:** Concentric or eccentric LVH can each be subclassified into 2 subgroups, yielding 4 distinct geometric patterns. Many subjects currently classified as having eccentric LVH can be reclassified into an indeterminate subgroup that has better LV function and comparable levels of biomarkers reflecting cardiac stress compared with those without LVH.

**Editor’s Comment:** Although the conventional classification of LVH allows for only 2 categories (concentric and eccentric), the authors reported an expanded classification scheme that, in essence, provides a better understanding of the degree to which hypertrophy is characterized by increased wall thickness, increased chamber size, or a combination of both. Particularly interesting is the identification of patients with indeterminate hypertrophy (increased mass despite normal concentricity and LVEDV). This very common pattern was associated with better LV ejection fraction than in those with increased LVEDV and with comparable natriuretic peptide and troponin T levels to those without LVH. Although no longitudinal data are available from which to assess the prognostic significance of this form of hypertrophy, these data raise the question of whether pathological LVH should be considered present only if LV mass is increased and there is evidence of increased wall thickness and ventricular dilation.16

**Impact of Longitudinal Myocardial Deformation on the Prognosis of Chronic Heart Failure Patients**

**Summary:** Several studies have suggested that longitudinal myocardial deformation indices (velocity, strain, and strain rate) are superior to left ventricular ejection fraction (LVEF) in identifying early changes in myocardial contractility. To clarify the clinical utility of these different markers, the authors compared the accuracy of peak systolic longitudinal velocity by tissue Doppler imaging as well as by strain and strain rate by speckle tracking with the left ventricular ejection fraction in predicting outcome in a heart failure population. They demonstrated that in this population, impaired longitudinal global strain by speckle tracking was greater than 9% was the best predictor of outcome, with an increase of the risk of cardiac events by 5.1. These results suggest that the use of longitudinal global strain by speckle tracking in assessing left ventricular contractility should be encouraged in clinical practice because of its good reproducibility and ability to better stratify the outcome of heart failure. Future studies should be performed to validate the potential impact of global longitudinal strain on medical decision-making.

**Conclusions:** In the heart failure population, longitudinal global strain by speckle tracking is superior to left ventricular ejection fraction and other longitudinal markers in identifying patients with poor outcome.

**Editor’s Comment:** Speckle-tracking echocardiography-based methods of assessing regional and global strain and strain rate are widely available and generally easily applied. Although such techniques provide information about circumferential, radial, and longitudinal strain, the clinical utility of regional and global longitudinal strain has been best established because these indices appear to be more sensitive to changes in myocardial contractility than ejection phase indices, such as ejection fraction. This study has argued that this superiority is clinically relevant in that global longitudinal strain better predicts outcomes in patients with chronic heart failure than left ventricular ejection fraction.16

**Prognostic Value of Right Ventricular Function in Patients After Acute Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention**

**Summary:** The prognosis of patients after acute myocardial infarction (AMI) is determined by the interaction of a large number of factors. Besides the importance of clinical parameters, several studies have described the importance of left ventricular function as one of the most important prognostic parameters. On the other hand, data on the association between right ventricular (RV) function and adverse events after AMI are scarce. In this study, the prognostic value of RV function in 612 consecutive patients with AMI treated with primary percutaneous coronary intervention and who underwent echocardiography within 48 hours of admission was evaluated. RV function was quantified with RV fractional area change, tricuspid annular plane systolic excursion, and RV strain. During a mean follow-up of 24 months, 86 patients reached the end point defined as a composite of all-cause mortality, reinfarction, and hospitalization for heart failure. RV fractional area change (hazard ratio, 0.96; 95% CI, 0.92–0.99) and RV strain (hazard ratio, 1.08; 95% CI, 1.03–1.13) were both independent predictors of the composite end point. In addition, RV strain provided incremental value to baseline clinical information, infarct characteristics, left ventricular function, and RV fractional area change for the prediction of the composite end point.

**Conclusions:** RV function provides strong prognostic information in patients treated with primary percutaneous coronary intervention for AMI.

**Editor’s Comment:** Sensitive imaging techniques such as T2-weighted cardiovascular magnetic resonance have identified a significant proportion of patients with MI who experience RV involvement. The authors applied contemporary echocardiography techniques to measure RV function, which were reportedly feasible in the majority of patients, to further advance our appreciation of the influence of the RV on outcomes after MI. After adjusting for factors known to influence outcome, such as left ventricular ejection fraction, RV functional measures had incremental prognostic value for the composite end point of mortality, reinfarction, and hospitalization for heart failure. These data suggest that therapeutic approaches to support RV recovery warrant further investigation to improve outcomes after acute coronary syndrome.20

**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, ~30% of patients do not respond to this sophisticated method due to the presence of dyssynchrony. The use of speckle-tracking echocardiography allows for the quantification of dyssynchrony, which is a measure of the difference in timing of contraction between different segments of the heart. This method has been shown to be more effective than traditional echocardiographic methods in identifying patients who would benefit from resynchronization therapy. Therefore, the use of speckle-tracking echocardiography to assess dyssynchrony in patients with dilated cardiomyopathy is a promising approach for improving outcomes after heart failure treatment.
before irreversible changes in LVEF occur. Characteristics predicted preserved LVEF longitudinally over time. A new MRI method that identified abnormal myocardial tissue involvement revealed abnormal myocardial tissue in patients with nonischemic dilated cardiomyopathy using speckle-tracking echocardiography-derived radial strain. 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 the SD 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 segment 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 the authors’ knowledge, this study has provided 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 in selecting candidates for cardiac resynchronization therapy or when used as a surrogate marker of prognosis.

**Editor’s Comment:** Thus far, echocardiography has met its match in 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 demonstrated the dynamic nature of LV dyssynchrony during temporary and acute changes in LV loading status. These findings emphasize the importance of standardizing of echocardiographic assessment of LV dyssynchrony and the opportunity to derive predictive measures.

**Novel Approach to Early Detection of Doxorubicin Cardiotoxicity by Gadolinium-Enhanced Cardiovascular Magnetic Resonance Imaging in an Experimental Model**

**Summary:** This study explored the utility of a new MRI method for identifying subclinical cardiotoxicity due to doxorubicin chemotherapy. At present, surveillance strategies for doxorubicin cardiotoxicity involve serial assessments of left ventricular ejection fraction (LVEF) by radionuclide or echocardiographic techniques. However, these strategies identify the end result of doxorubicin injury late in its course, after such injury may be irreversible. The authors described a new MRI method that identified abnormal myocardial tissue characteristics early after doxorubicin exposure and before marked changes in LVEF. Moreover, an absence of change in MRI tissue characteristics predicted preserved LVEF longitudinally over time. These results suggest that new imaging strategies in human subjects may be used to identify early evidence of doxorubicin cardiac injury before irreversible changes in LVEF occur.

**Conclusions:** After doxorubicin exposure, low serial measurements of signal intensity after gadolinium-based contrast administration (Gd-SI) predict an absence of an LVEF drop or unanticipated death. An increase in Gd-SI after doxorubicin exposure forecasts a subsequent drop in LVEF as well as histopathological evidence of intracellular vacuolization consistent with doxorubicin cardiotoxicity.

**Editor’s Comment:** Although the incidence of clinically apparent cardiomyopathy due to doxorubicin exposure may be relatively low, those affected may experience devastating and irreversible heart failure. The authors measured myocardial Gd-SI in a small animal model, showing increased Gd-SI before LVEF reduction or unanticipated death after doxorubicin exposure. These data suggest that cardiovascular magnetic resonance-based tissue characterization identifies early evidence of anthracycline-induced myocardial injury. Further preclinical and clinical studies are warranted to test the value of such measures in demonstrating reversible injury and in testing novel cardioprotective approaches.

**Quantification of Diffuse Myocardial Fibrosis and Its Association With Myocardial Dysfunction in Congenital Heart Disease**

**Summary:** There is growing recognition that progressive myocardial dysfunction in patients with congenital heart disease contributes substantially to clinical heart failure, arrhythmia, and mortality. MRI with late gadolinium enhancement has been used to demonstrate areas of replacement fibrosis in several subgroups of congenital heart disease, confirming that myocardial fibrosis is a likely final common pathway in these patients. However, late enhancement identifies dense replacement fibrosis and is not as amenable to detecting smaller amounts of diffuse, microscopic fibrosis. To quantify myocardial fibrosis, the authors used a modified Look-Locker sequence to quantify a fibrosis index based on T1 times for a single short-axis plane of the systemic ventricle before and after administration of gadolinium-based contrast. In 50 patients with congenital heart disease, the fibrosis index was significantly elevated in the patients compared with normal controls and especially elevated in patients with a systemic right ventricle and those with cyanosis. The fibrosis index correlated with end-diastolic volume index and ventricular ejection fraction but not with age. Values for patients with congenital heart disease were largely similar to patients with cardiomyopathy. The findings lay the groundwork for further investigation on pathophysiology and treatment of heart failure, specifically in congenital heart disease.

**Conclusions:** Patients with adult congenital heart disease have evidence of diffuse, extracellular matrix remodeling similar to patients with acquired heart failure. The fibrosis index may facilitate studies on the mechanisms and treatment of myocardial fibrosis and heart failure in these patients.

**Editor’s Comment:** The traditional technique for imaging myocardial fibrosis with T1-weighted cardiovascular magnetic resonance with late gadolinium enhancement performs well in demonstrating discrete infarct scar or replacement fibrosis. The authors applied the emerging technique of T1 mapping, a quantitative approach that may better demonstrate diffuse interstitial fibrosis in a cohort of patients with congenital heart disease. A fibrosis index, based on T1 measurements adjusted for hematocrit level, was found to be higher in patients compared with healthy controls and was particularly elevated in the myocardium of systemic right ventricles and patients with cyanotic congenital heart disease. Further studies are warranted to understand the predictive value of this index for clinical sequelae such as systemic right ventricular failure and ventricular arrhythmia.

**Impaired ATP Kinetics in Failing In Vivo Mouse Heart**

**Summary:** Energy metabolism fuels ongoing myocardial contraction, and altered metabolism may contribute mechanistically to several cardiac diseases, including heart failure. 31P magnetic resonance spectroscopy is the only means to noninvasively quantify the levels of myocardial high-energy phosphates, adenosine 5’-triphosphate (ATP), and creatine phosphate. Magnetization transfer 31P magnetic resonance spectroscopy methods were adopted in recent years to measure the rate of ATP turnover in the human heart.
Such $^{31}$P magnetic resonance spectroscopy techniques, when combined with MRI approaches, offer a powerful means to assess cardiac energy metabolism, structure, mass, and contractile function in the same examination. Murine models are increasingly used to probe molecular mechanisms of human disease because of the possibility of creating specific transgenic lines. However, the small size ($\sim 0.1$ g) and high rate ($\sim 600$ beats/min) of the mouse heart present significant challenges for noninvasive imaging approaches. In this study, the first noninvasive in vivo measures of the rate of ATP synthesis through creatine kinase (CK), the major myocardial energy reserve, in the murine heart were reported. The authors demonstrated that ATP turnover rates in normal and failing mouse hearts are comparable to those reported in human hearts. This validated, noninvasive approach to measuring ATP synthesis rates through CK in the intact mouse can be combined with anatomic and functional measures in the same examination and be repeated over time as pathology develops. The observations demonstrated that murine models recapitulate several fundamental aspects of human myocardial energy metabolism in vivo and support their use to probe specific metabolic contributions to the development and progression of heart failure.

**Conclusions:** Despite small size and high murine heart rate, the ATP synthesis rate through CK is similar in vivo in murine and human hearts and comparably reduced in heart failure. Because murine thoracic aortic constriction shares fundamental energetic similarities with human heart failure, this model and new magnetic resonance spectroscopy approach promise a powerful means to noninvasively probe altered energetics in heart failure.

**Editor’s Comment:** Despite a vast armamentarium of therapies ranging from neurohormonal modulation to resynchronization, mortality in heart failure remains high. Heart failure as a fundamental problem of energetics has gained increased attention with advances in cardiovascular magnetic resonance spectroscopy. One such advance by these authors validates a new, more time-efficient technique to measure in vivo in the murine heart the rate constant of the equation converting phosphocreatine to ATP, or CK flux. In a murine heart failure model, the technique yielded very comparable reduction in $k_f$, previously measured in humans by the same group. Such translational validity holds promise for drug development targeting impaired myocardial energetics with this in vivo cardiovascular magnetic resonance spectroscopy approach as a reliable technique for serial CK flux analysis.

**Relation Between Right Ventricular Function and Increased Right Ventricular $^{18}$FFluorodeoxyglucose 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-sided 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 fluorodeoxyglucose 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.

**Influence of Diabetes Mellitus on Prognostic Utility of Imaging of Myocardial Sympathetic Innervation in Heart Failure Patients**

**Summary:** Patients with diabetes mellitus have accelerated progression of heart failure (HF). The present study examines the implications for HF progression of cardiac sympathetic denervation, assessed by I-123 metaiodobenzylguanidine (MIBG) imaging. HF progression (defined as an increase in New York Heart Association functional class) during a median follow-up of 17 months was examined in 343 patients with diabetes and 618 patients without diabetes with New York Heart Association class II or III HF and a left ventricular ejection fraction $\leq 35\%$. By multivariable Cox proportional hazards model, the variables associated with time to an HF progression event were b-type natriuretic peptide level, left ventricular ejection fraction, late I-123 MIBG heart-to-mediastinum (H/M) ratio, the interaction term diabetes mellitus with late H/M ratio, early H/M ratio, and New York Heart Association classification. The presence of a late H/M ratio $<1.6$ was associated with a 2.99-fold increase in the risk of HF progression in patients with diabetes. Conversely, there was no difference in the risk of HF progression between patients with and without diabetes if the late H/M ratio was $\geq 1.6$, indicating relatively preserved cardiac sympathetic innervation. These findings indicate that cardiac sympathetic nerve dysfunction increases the risk of HF progression in patients with diabetes mellitus. Therefore, treatment designed to prevent or ameliorate cardiac sympathetic denervation in patients with diabetes (eg, $\beta$-adrenergic-blocking drugs) may provide additional benefit for the prevention of HF progression beyond those therapies focused primarily on treatment of diabetes.

**Conclusions:** The combination of diabetes mellitus and I-123 MIBG H/M ratio is an independent predictor of HF progression, confirming the high risk of patients with diabetes with impaired cardiac sympathetic nerve function.

**Editor’s Comment:** Diabetes wreaks havoc on the cardiovascular system, and patients with diabetes consistently fare worse with conditions such as HF compared with individuals without diabetes. The authors shed insight into this difference using I-123 MIBG imaging to measure cardiac adrenergic activity. In nearly 1000 patients with HF, reduced cardiac sympathetic nerve function was shown to predict greater 2-year rates of HF progression, which were still higher with the added feature of diabetes. For a group of patients with often insidious progression of cardiovascular disease, this work offers a window into a potential mechanism for disease progression. Targeting cardiac neuropathy may, in turn, offer hope in reducing cardiac morbidity and mortality for patients with diabetes.

**Echocardiographic Evaluation of Hemodynamics in Patients With Decompensated Systolic Heart Failure**

**Summary:** The assessment of hemodynamics in patients with acute decompensated heart failure can be of value in their treatment. The authors evaluated the accuracy of Doppler echocardiography in estimating left and right ventricular hemodynamics in 79 patients with unstable heart failure. The technique had a good accuracy in the estimation of stroke volume, pulmonary artery systolic and diastolic pressure, and mean right atrial pressure. Several Doppler indices, including tissue Doppler imaging, had good accuracy in identifying patients with pulmonary capillary wedge pressure $>15$ mm Hg. In addition, the recent American Society of Echocardiography/European Association of Echocardiography guidelines were highly accurate in
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 in the diagnosis of endomyocardial fibrosis (EMF), using surgical specimens as the standard method. LGE cardiovascular magnetic resonance confirmed the diagnoses in patients with EMF 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. This study has provided evidence that LGE cardiovascular magnetic resonance is a reliable diagnostic tool to confirm EMF.

Conclusions: This study provides evidence that LGE cardiovascular magnetic resonance is useful in the diagnostic and prognostic assessment 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 research focus for MRI. Standard LGE imaging as well as several other MRI sequences have been developed, and this study, in a small population, suggests that MRI will become an essential component of patient care.

Prognostic Value and Determinants of a Hypointense Infarct Core in T2-Weighted Cardiac Magnetic Resonance in Acute Reperfused ST-Elevation-Myocardial Infarction

Summary: Cardiovascular magnetic resonance (CMR) can provide a wide range of prognostic information in acute ST-segment elevation myocardial infarction by detecting infarct size, microvascular obstruction, and myocardial salvage. Additionally, a hypointense core of infarcted myocardium in T2-weighted CMR has been used as a noninvasive marker for idiopathic myocardial hypertrophy. However, the clinical significance of such findings has not yet been established. This study has been the largest study thus far to assess determinants and the prognostic significance of hypointense infarct cores in T2-weighted CMR. A hypointense core within the area at risk of reperfused infarcted myocardium in T2-weighted CMR is a frequent finding in reperfused patients with ST-segment elevation myocardial infarction and is closely related to infarct size, impaired left ventricular function, and late microvascular obstruction. Moreover, hypointense infarct cores are a strong indicator of major adverse cardiac events at 6-month clinical follow-up and may serve as a new CMR marker of severe reperfusion injury. However, further validation is necessary to conclusively ascertain the relationship between hypointense infarct cores and idiopathic myocardial hypertrophy, and large multicenter studies are warranted to further investigate the prognostic significance of hypointense infarct cores.

Conclusions: A hypointense infarct core within the area at risk of reperfused infarcted myocardium on T2-weighted CMR is closely related to infarct size, microvascular obstruction, and impaired left ventricular function, with subsequent adverse clinical outcome.

Editor’s Comment: Among various predictors of post-ST-segment elevation myocardial infarction outcome after coronary revascularization, the extent of damage to the affected myocardium has gained increasing attention, thanks to more-precise approaches to characterize myocardial injury. One such approach is T2-weighted CMR in conjunction with late gadolinium enhancement imaging. The authors implemented these techniques in a 2-center study of patients with ST-segment elevation myocardial infarction after primary percutaneous coronary intervention, focusing on the hypointense infarct core. There was incremental value in identifying such a core—a distinct region from areas of microvascular obstruction by late gadolinium enhancement—to predict death, reinfarction, and new congestive heart failure within 6 months. These data suggest that greater attention should be paid to the myocardium downstream for both postmyocardial infarction risk stratification and development of risk reduction strategies.

Echocardiographic Indices Do Not Reliably Track Changes in Left-Sided Filling Pressure in Healthy Subjects or Patients With Heart Failure With Preserved Ejection Fraction

Summary: Several modalities of echocardiography, including Doppler echocardiography, tissue Doppler imaging, and color M-mode echocardiography, have shown promise in the estimation of left-sided filling pressures. Two such indices, early filling-to-early diastolic mitral annular velocity ratio (E/E') and early filling-to-flow propagation velocity ratio (E/Vp), have received recognition for their utility in the 1-time estimation of left-sided filling pressures in healthy subjects as well as in select populations with cardiovascular disease. Some have extrapolated these findings, proposing the serial use of these indices to monitor changes in left-sided filling pressures in healthy research subjects or to titrate medical therapy in patients with heart failure. However, doing so would require demonstration that changes in noninvasive indices accurately track changes in left-sided filling pressures in healthy research subjects or to titrate medical therapy in patients with heart failure. However, doing so would require demonstration that changes in noninvasive indices accurately track changes in left-sided filling pressures within individuals as filling pressures vary. To test this hypothesis, the authors made multiple, simultaneous measurements of E/E', E/Vp, and pulmonary capillary wedge pressure within healthy subjects and outpatients with heart failure with preserved ejection fraction (HFP EF) as preload was manipulated using lower-body negative pressure and rapid saline infusion. The key finding was that as left-sided filling pressures were manipulated, the relationships between E/E' and pulmonary capillary wedge pressure and E/Vp and pulmonary capillary wedge pressure were highly variable, with individual subject linear regression slopes ranging from steeply negative to steeply positive and coefficients of determination ranging from very low to very high. In this study, noninvasive indices did not adequately track changes in left-sided filling pressures because these pressures varied within individual subjects. These findings raise concern about the use of these indices in research studies with healthy volunteers or to titrate medical therapy in patients with HFP EF.

Conclusions: Within individual subjects, the noninvasive indices E/E' and E/Vp do not reliably track changes in left-sided filling pressures as these pressures vary, precluding the use of these techniques in research studies with healthy volunteers or the titration of medical therapy in patients with HFP EF.

Editor’s Comment: Publication bias toward positive results is well recognized, but this study is an example of the usefulness of a negative study outcome. In this specific case, the authors found that...
noninvasive indices previously suggested to track changes in left-sided filling pressures in volunteers do not behave similarly in patients with HFrEF because these pressures varied within individual subjects. Previously, it was suggested that these indices could be used to titrate medical therapy in patients with HFrEF. Considering the complex hemodynamic situation in heart failure and the dynamic nature of many of the factors determining filling pressure, such variability seems plausible.30

Prognostic Value of Routine Cardiac Magnetic Resonance Assessment of Left Ventricular Ejection Fraction and Myocardial Damage: An International, Multicenter Study

Summary: Cardiovascular magnetic resonance (CMR) is considered the reference standard for assessment of left ventricular ejection fraction (LVEF) and myocardial damage. However, few studies have evaluated the relationship between CMR findings and patient outcome, and of these, most are small and none multicenter. The authors performed an international, multicenter study to assess the prognostic importance of routine CMR in patients with known or suspected heart disease. Consecutive patients from 10 centers in 6 countries who underwent routine CMR assessment of LVEF and myocardial damage by cine- and delayed-enhancement (DE) CMR, respectively, were screened. A total of 1560 patients were enrolled (age, 59±14 years; 70% men). Mean LVEF was 45±18%, and 1049 (67%) patients had hyperenhanced tissue on DE CMR, indicative of damage. During a median follow-up time of 2.4 years, 176 (11.3%) patients died. Patients who died were more likely to be older, have coronary artery disease, have lower LVEF, and have more segments with hyperenhanced tissue. In multivariable analysis, age, LVEF, and number of segments with hyperenhanced tissue were independent predictors of mortality. The number of segments with hyperenhanced tissue provided incremental prognostic value beyond clinical data and LVEF. Even in patients with near-normal LVEF, significant damage identified a cohort at high risk for early mortality. In this study, the authors demonstrated that in a large population from several CMR centers, unique CMR information on myocardial damage from ischemic and nonischemic etiologies provides independent and incremental prognostic value.

Conclusions: Both LVEF and amount of myocardial damage as assessed by routine CMR are independent predictors of all-cause mortality. Even in patients with near-normal LVEF, significant damage identifies a cohort with a high risk for early mortality.

Editor’s Comment: This article has presented a prime example of a much-needed assessment of the association of a biomaging marker with clinical outcomes in a large multicenter population, thereby validating the imaging-based measure as a surrogate marker for mortality. Specifically, the authors assessed the association of myocardial DE as measured by CMR with mortality and demonstrated that DE is incremental to LVEF and clinical data in patients with known or suspected heart disease. These observations can be explained by the pathophysiology of DE, which is an unspecific marker of myocardial viability that can be observed in both acutely and chronically injured myocardium and in several other myocardial processes that cause myocardial necrosis, infiltration, or fibrosis, including myocarditis, hypertrophic cardiomyopathy, amyloidosis, and sarcoidosis. This study has provided the prerequisites for further studies to assess in more detail the association of coronary artery disease, including nonobstructive disease, with DE and studies assessing the effect of therapy on DE, with DE serving as a surrogate marker for mortality.31

Assessment of Diffuse Myocardial Fibrosis in Rats Using Small-Animal Look-Locker Inversion Recovery T1 Mapping

Summary: The development of diffuse myocardial fibrosis (DMF) has been identified as a crucial step in the progression of myocardial disease toward heart failure. Despite this knowledge, fibrotic burden of the heart is not a routine component of clinical decision-making because noninvasive quantification of DMF has not been routinely possible. Extracellular volume (ECV) can be determined by the use of T1 mapping MRI and has been proposed as a marker for collagen content of the myocardium. During the past few years, robust T1 mapping techniques for human applications have become available for most MRI systems. Initial clinical studies showed promising results, suggesting the clinical potential of this approach. The results of this study on ECV changes in a small animal model of mild angiotensin-2-induced DMF further support the validity of this concept, demonstrating significant increases of ECV in rats subjected to a 2-week infusion of angiotensin-2. There was a moderate correlation of ECV and collagen volume fraction as assessed by histological analysis, The MRI-derived ECV can be noninvasively estimated in both humans and rodents, supporting serial in vivo studies of fibrosis in suitable preclinical models of disease to test novel therapeutic strategies that can be translated to clinical evaluation.

Conclusions: In a small animal model of left ventricular hypertrophy, contrast-enhanced T1 mapping can be used to detect DMF by quantification of myocardial ECV.

Editor’s Comment: DMF is an important marker in many cardiac diseases and could be specifically useful to assess the progression of myocardial disease toward heart failure with an emphasis on diastolic dysfunction and left ventricular remodeling. However, because detection and quantification of DMF has been limited so far, the need for biopsy for its assessment, this measure has not been clinically available. With the progression of cardiovascular magnetic resonance technology, T1 mapping has been a promising candidate sequence to describe DMF. Several animal and a few patient studies have demonstrated the feasibility of this technique to detect the presence and, less accurately, the extent of myocardial fibrosis compared with histology. This study has provided data in small animals that demonstrate the feasibility of T1 mapping to potentially describe serial changes in the presence and extent of DMF as measured by the extent of ECV after angiotensin-2 infusion. If these pilot data are confirmed, a T1 mapping of DMF could be an important imaging marker to test novel therapeutic strategies targeting DMF and heart failure in both animal models and patients. An accurate noninvasive method for DMF assessment could transform cardiology.32

PET Imaging May Provide a Novel Biomarker and Understanding of Right Ventricular Dysfunction in Patients With Idiopathic Pulmonary Arterial Hypertension

Summary: This is a comprehensive study in patients with idiopathic pulmonary arterial hypertension (PAH) (New York Heart Association functional class I/II). All the patients underwent MRI, right heart catheterization, quantification of myocardial blood flow, quantification of myocardial glucose uptake, and cardiopulmonary exercise testing. The study revealed that PET scanning with 18F-fluorodeoxyglucose appears to be a feasible modality for quantifying right ventricular (RV) blood flow and RV metabolism in patients with idiopathic pulmonary hypertension. An increased metabolic rate of glucose uptake in the RV presumably indicates early RV functional impairment. The shift in myocardial glucose uptake may be an early marker of RV dysfunction and possibly a preclinical marker before overt RV failure, given that RV function on MRI in the current study was largely preserved and that most patients were in New York Heart Association functional class I/II. The relations observed support the need for further investigation of myocardial glucose uptake as a novel early biomarker that could be a therapeutic target in the treatment and monitoring of PAH. In addition, the study demonstrated a trend toward negative correlation with maximum oxygen consumption, suggesting that this finding may have some prognostic impact. Maximum oxygen consumption...
is considered a strong predictor of survival in patients with PAH. Monitoring myocardial glucose uptake level may help to optimize treatment to improve function and outcome.

**Conclusions:** PET scanning with $^{15}$N-NH$_3$ and $^{18}$F-fluorodeoxyglucose is a feasible modality for quantifying RV blood flow and metabolism in patients with idiopathic PAH.

**Editor's Comment:** The field of using fluorodeoxyglucose or similar tracers to investigate glucose metabolism in structural myocardial, valve, and coronary disease is rapidly growing. This study is in line with a few other publications in the assessment of increased RV uptake in patients with PAH. Together with the finding of increased maximum oxygen consumption, this study provides a comprehensive assessment with biologically plausible findings for early detection and markers of RV stress, including dysfunction and failure. Given that other available objective markers of pulmonary hypertension, such as pulmonary artery pressure and pulmonary artery dimensions, do not change before significant disease manifestation, metabolic measures would provide an ideal marker for early detection for PAH.\(^\text{33}\)

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

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

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

**Editor's Comment:** This study has provided insight into the importance of hemodynamic conditions, especially the importance of sufficient unloading of the LV and concomitant right ventricular function improvement in securing sustained benefits from LVAD. This confirms other studies that also identified that small LV size or early systolic equalization of right ventricular and right atrial pressure demonstrated by echocardiography is associated with increased morbidity and mortality. It appears that a variety of echocardiographic measures predict early and mid-term adverse outcomes incrementally to blood biomarkers or hemodynamic variables.\(^\text{34}\)

### Cardioprotective Effects of Ischemic Postconditioning in Patients Treated With Primary Percutaneous Coronary Intervention, Evaluated by Magnetic Resonance

**Summary:** Acute restoration of myocardial blood flow with primary percutaneous coronary intervention (PCI) in itself jeopardizes the cardiomyocytes. In some cases, this phenomenon accounts for 50% of the final size of the myocardial infarction. Therefore, it is important to look for means to protect the myocardium during reperfusion. Ischemic postconditioning has been suggested as such a method. Few small studies have demonstrated a beneficial effect of ischemic postconditioning, but the effect on the final infarct size only has been assessed in 38 patients with perfusion defect index measured by scintigraphy as a surrogate measurement for the infarct size. Ischemic postconditioning is simple, cheap, not time consuming, and a safe adjuvant to primary PCI, and the method can be introduced in the catheterization laboratories almost overnight. However, the possible introduction of this modality in the authors' view should be demonstrated in a substantial number of patients before taken into consideration. With the use of cardiac magnetic resonance to measure final infarct size in 86 patients, this study demonstrated a decrease in infarct size of 18% with ischemic postconditioning. Being the first to evaluate effect of ischemic postconditioning by cardiovascular magnetic resonance, the authors believed that this study makes an important contribution. Furthermore, it is the first, to the authors' knowledge, to suggest an effect on functional status evaluated by New York Heart Association classification.

**Conclusions:** Mechanical postconditioning reduces infarct size in patients with ST-segment elevation myocardial infarction treated with primary PCI. The impact of mechanical postconditioning seems to be independent of the size of myocardium at risk.

**Editor's Comment:** This article constitutes another great example of using delayed enhancement as measured by cardiac MRI as a surrogate end point. Specifically, the authors assessed the effect of ischemic postconditioning after PCI on myocardial salvage. Moreover, the authors proved that this also resulted in improved clinical outcomes, with the number of patients developing heart failure nearly halved. Interestingly, other investigators did not find these effects by MRI 6 to 9 days after PCI indicating that the effect manifests sometimes after an acute injury. Positive long-term effects >3 years of ischemic postconditioning have also been described. Thus, evidence is mounting that ischemic postconditioning is a favorable and simple intervention.\(^\text{35}\)

### Assessment of Left Ventricular Function in Older Medicare Beneficiaries With Newly Diagnosed Heart Failure

**Summary:** Two of 5 Medicare beneficiaries do not undergo assessment of left ventricular systolic function after a new diagnosis of heart failure. Although the proportion of patients who undergo assessment of left ventricular systolic function has increased over time, women, black patients, older patients, and outpatients are the least likely to undergo testing.

**Conclusions:** Nearly 40% of Medicare beneficiaries do not undergo assessment of left ventricular function when given a new diagnosis of heart failure. Quality improvement strategies are needed to optimize the care of these patients, especially in outpatient settings.

**Editor's Comment:** This study has confirmed previous observations from stable inpatient and acute heart failure presentation in the emergency department that assessment and follow-up of patients with newly diagnosed heart failure is suboptimal. The specific goal of this study was to assess predictors for use of standard assessment of systolic left ventricular function, a level Ia recommendation in an analysis of Centers for Medicare & Medicaid Services data from
1991 through 2008. Surprisingly, the number of patients with incident heart failure decreased from 45 005 in 1995 to 32 629 in 2007. The data also show that although overall imaging use increased to 60%, use was 4 times less likely in outpatients presenting with de novo heart failure. Efforts to optimize adequate follow-up by specialists are warranted.36

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