Circ Heart Fail Editors’ Picks

Most Important Papers in Heart Failure and Imaging

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The following are highlights from Circulation: Heart Failure Topic Review. This series will summarize the most important manuscripts, as selected by the editors, that have been published in the Circulation portfolio. The objective of this series is to provide our readership with a timely comprehensive selection of important papers that are relevant to the heart failure audience. The studies included in this article represent the most noteworthy research in the areas of heart failure and imaging. (Circ Heart Fail. 2012;5:e4-e14.)

Measurement Precision in the Optimization of Cardiac Resynchronization Therapy

Summary: Cardiac resynchronization therapy improves morbidity and mortality in appropriately selected patients. Whether further clinical benefit is possible with atroventricular and interventricular pacing interval optimization remains unclear. Tools to assess the statistical significance of the measured optimization data have not been available previously. In the study reported here, an objective methodology for quantifying the statistical precision of estimated optimum pacing intervals was developed and applied to a number of commonly used optimization techniques. Many of the techniques did not yield statistically significant data in a majority of patients referred for atroventricular and interventricular interval optimization, a finding that raises questions about the ability of pacing interval optimization to enhance clinical outcomes. The data demonstrate that accepting an estimated optimum interval without consideration of its statistical significance can result in worse cardiac function than default settings and can lead to the erroneous conclusion that the physiological optimum has changed over time. These results highlight the importance of evaluating the precision of measured data when conducting pacing interval optimization for the individual patient and when interpreting the results of clinical trials.

Conclusions: Consideration of statistical significance is critical for validating clinical optimization data in individual patients and for comparing competing optimization techniques. Accepting an estimated optimum without knowledge of its precision can result in worse cardiac function than default settings and a misinterpretation of observed changes over time. In this study, only impedance cardiography yielded statistically significant AV and VV interval optimization data in the majority of patients.1

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 30–40% of patients receiving cardiac resynchronization therapy 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 cardiac resynchronization therapy (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 lack of constraint by the coronary venous anatomy. The authors found that zones of slow conduction could be identified using delayed-enhancement cardiac magnetic resonance in patients with an ischemic heart failure etiology but not in nonischemic cardiomyopathy. The acute 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 lack of response to CRT and reinforces the need for positioning the LV lead on an individual basis.

Conclusions: Endocardial LV pacing appears to be superior to conventional CRT, although the optimal site varies between subjects and is influenced by pacing within areas of slow conduction. Delayed-enhancement cardiac magnetic resonance was a poor predictor of zones of slow conduction in nonischemic patients.2

Cardiac Sympathetic Reserve and Response to Cardiac Resynchronization Therapy

Summary: Heart failure is associated with disregulated autonomic function with abnormally activated sympathetic and altered parasympathetic tone. The present study reports 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 iodine-123 metaiodobenzylguanidine (123I-MIBG) heart/mediastinum ratio and attenuated heart/mediastinum washout rate, determined by 123I-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 subjects 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
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 dysynchrony 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 or not 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 indicate that the ventricle must be dyssynchronous but also viable, as reflected by contractile function, to benefit from CRT. These findings suggest that mechanical dyssynchrony and contractile function may be 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.4

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 beneficial effects of cardiac resynchronization therapy on long-term survival are influenced by several pathophysiological factors. The present study demonstrated the relative merits of left ventricular (LV) dyssynchrony, LV lead position, and myocardial scar to predict long-term outcome of ischemic heart failure patients 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 is placed were evaluated. In addition, the LV lead position was derived from chest radiography 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 patients (68%), 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 patients (22%) 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 ischemic heart failure patients 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.5

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-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 nor LV reverse remodeling. Among several factors that determine a favorable response to CRT, the amount of LV fibrosis as assessed, for example, with cardiac magnetic resonance has been shown to be an important issue. The current study demonstrates 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 heart failure patients, myocardial ultrasound reflectivity was found to be the only independent determinant of LV reverse remodeling after CRT. In the nonischemic subgroup of heart failure patients, myocardial ultrasound reflectivity was still an independent predictor of CRT response. Several pathophysiological issues must be addressed to optimize selection of CRT patients. 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 ischemic and nonischemic patients.6

Evaluation of Left Ventricular Dyssynchrony by Onset of Active Myocardial Force Generation: A Novel Method That Differentiates Between Electric 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 patient selection. In this animal study, the authors introduce 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 activation time, regional AFG may serve as a better measure of the direct electric activation delay between the left ventricular segments. A patient with synchronous left ventricular 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 the
present study, the authors showed that ejection phase echocardiographic dyssynchrony indices are dependent on regional contractile state (ischemia) and load as well as 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 was not dependent on load or contractile state. The current limitations of the proposed AFG method are that it requires measurements of left ventricular 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 is a method that should be further explored in patients undergoing left heart catheterization.

Conclusions: Onset AFG was an accurate marker of myocardial electric activation and was superior to shortening velocity and strain. Identification of electric dyssynchrony by onset AFG may be feasible clinically using left ventricular pressure-strain analysis.7

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 provides important indices of cardiac function. Earlier studies have yielded conflicting evidence on whether or not 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 sought to study 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 displacement field within the left ventricle. The results of this study indicate that CRT acutely improves hemodynamic parameters without improving LV rotation mechanics. This suggests that improvement in LV rotation mechanics appears to be a 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. These results suggest that LV rotation mechanics is an index of global LV function, which requires coordination of all regions of the left ventricle, and improvement in LV rotation mechanics appears to be a specific but insensitive index of acute hemodynamic response to CRT.8

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

Summary: The criteria for selecting heart failure patients for cardiac resynchronization therapy (CRT), namely ejection fraction, New York Heart Association 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, that is, 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 operative characteristic curve analysis demonstrated that an optimal cutoff value of 25.5° 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-computed tomography–based phase measurements in selecting patients for CRT. IVD probably is an important predictor of response to CRT. The threshold for IVD determined by receiver operating characteristic analysis in the present 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.9

Mechanisms of Abnormal Systolic Motion of the InterventricularSeptum 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, respectively. It has not been definitely determined if this abnormal motion is due to active septal contraction or if it represents passive motion caused by an early rise in right ventricular pressure that pushes the septum leftward. The recent interest in quantification of dyssynchrony in patients who are candidates for cardiac resynchronization therapy has highlighted the importance of this distinction: If prejection septal motion is due to active contraction, it reflects timing of septal activation and should be included in left ventricular dyssynchrony 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 and left ventricular pressures by micromanometers. The report concludes that the abnormal septal motion during prejection is a result of active septal contraction, unopposed by the late-activated left ventricular lateral wall. Whereas the magnitude of the prejection septal motion was modulated by changes in right and left ventricular loading, onset of septal shortening reflected septal activation regardless of loading conditions. These experimental data suggest that onset of prejection shortening rather than ejection phase indices should be used for timing of septal activation.

Conclusions: Leftward prejection motion of the septum during left bundle-branch block is mainly a result of active septal contraction, whereas alterations in diastolic ventricular pressures modulate the amplitude of this motion. The findings imply that the prejection phase should be included when assessing left ventricular dyssynchrony.10

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 heart failure patients for cardiac resynchronization therapy (CRT).
The authors applied phase analysis of gated single-photon emission computed tomography (g-SPECT), using a novel single-injection protocol, to prospectively measure left ventricular (LV) synchrony before and immediately after clinically indicated biventricular (BiV) pacemaker implantation. Patients with deteriorated LV synchrony acutely had worse outcome, defined as a composite of cardiac death, heart failure hospitalization, appropriate implantable cardioverter-defibrillator discharge, and deactivation of BiV pacing for worsening symptoms. Furthermore, the acute response to CRT was accurately predicted by using baseline g-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 g-SPECT was successfully used to predict acute change in LV synchrony and patient outcome after CRT.11

**Lack of Diastolic Reserve in Patients With Heart Failure and Normal Ejection Fraction**

**Summary:** The genesis of symptoms of breathlessness in patients with heart failure and normal ejection fraction has been poorly elucidated. Although most of these patients are breathless only on exertion, most investigations of heart failure and normal ejection fraction have focused on cardiac function at rest. The authors attempted to characterize the pathophysiological basis of this exercise-induced breathlessness by use of dobutamine stress echocardiography and tissue Doppler imaging. The study suggests that exercise intolerance, as measured by the 6-minute walk distance, in patients with heart failure and normal ejection fraction is related in part to stress-induced impairment in the diastolic relaxation of the left ventricle with resultant increase in the left ventricular end-diastolic pressure. Overt global or regional systolic dysfunction because of stress-induced ischemia was not seen in our patients. The mitral annular systolic velocity at rest is lower in these patients, suggesting an impaired long-axis function. However, this increases with stress, similar to controls. Dobutamine stress echocardiography unmasked the diastolic abnormality and excluded significant inducible ischemia as the cause of these symptoms. Thus, routine stress echocardiography may be useful in fully evaluating these patients. Exercise may be a more appropriate stressor than dobutamine.

**Conclusions:** Impaired diastolic reserve results in stress-induced increase in the left ventricular end-diastolic pressure in patients with heart failure and normal ejection fraction, giving rise to exercise intolerance.12

**Characteristics and Clinical Significance of Late Gadolinium Enhancement by Contrast-Enhanced Magnetic Resonance Imaging in Patients With Hypertrophic Cardiomyopathy**

**Summary:** Myocardial late gadolinium enhancement (LGE) on contrast-enhanced MRI of patients with hypertrophic cardiomyopathy has been suggested to represent intramyocardial fibrosis. The authors explored the relation between LGE among 424 patients with hypertrophic cardiomyopathy and their genetic testing status, presence of severe symptoms, ventricular arrhythmias, or occurrence of sudden cardiac death. Two hundred thirty-nine patients (56%) had LGE on contrast-enhanced MRI of patients with hypertrophic cardiomyopathy and their genetic testing status, presence of severe symptoms, ventricular arrhythmias, or occurrence of sudden cardiac death and/or implantable cardioverter-defibrillator discharge. If replicated, LGE may be considered an important risk factor for sudden death in patients with hypertrophic cardiomyopathy.

**Conclusions:** In patients with hypertrophic cardiomyopathy, presence of LGE on contrast-enhanced MRI was common and more prevalent among gene-positive patients. LGE was not associated with severe symptoms, but LGE was strongly associated with surrogates of arrhythmia and remained a significant associate of subsequent sudden cardiac death and/or implantation of cardioverter-defibrillator discharge. If replicated, LGE may be considered an important risk factor for sudden death in patients with hypertrophic cardiomyopathy.

**The Unrecognized Burden of Osteoporosis-Related Vertebral Fractures in Patients With Heart Failure**

**Summary:** Heart failure (HF) is associated with several factors that contribute to both reduced bone mineral density and increased risk of osteoporosis-related fractures. The authors conducted a cross-sectional study in patients attending an HF clinic in Edmonton, Canada, to describe the prevalence and predictors of the most common osteoporotic fracture, vertebral compression fractures (VCF), in patients with HF. The primary outcome was board-certified radiologist–documented VCF on chest radiography. Of the 623 patients, 12% had a VCF on chest radiography, and 55% of these were multiple fractures; few were receiving treatment for osteoporosis. Significant predictors of VCF included atrial fibrillation and lipid-lowering therapy, and these remained significant even after accounting for female sex, weight, and other clinical predictors for osteoporotic fracture. The authors conclude that chest radiograph reports may represent an important case-finding tool for osteoporosis-specific VCF, particularly in HF patients with atrial fibrillation in whom chest radiographs are commonly ordered. Additionally, atrial fibrillation is a previously unrecognized risk factor independently associated with VCF.

**Conclusions:** About one-tenth of HF patients had a chest radiograph–documented VCF, and half of those with VCF had multiple fractures; most (85%) were not receiving an osteoporosis-specific therapy. A previously unrecognized risk factor—atrial fibrillation—was found to be independently associated with VCF. Chest radiograph reports may represent an important case-finding tool for osteoporosis-specific VCF, particularly in HF patients with atrial fibrillation.14

**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 β-thalassemia major patients, in whom iron accumulation leads to damage in the liver, heart, and endocrine organs. Myocardial iron is assessed clinically with the cardiovascular magnetic resonance relaxation parameter T2*. This study describes the calibration of cardiovascular magnetic resonance relaxation against human iron concentration and the iron distribution throughout the heart under conditions of iron overload. A strong correlation was observed between cardiovascular magnetic resonance relaxation measurements and biochemically derived tissue iron concentration in 12 postmortem human hearts from transfusion-dependent patients, leading to a clinical calibration equation of [Fe]=[45.0×(T2*)]−1.12, where [Fe] is measured in milligrams per gram dry weight and T2* is measured in milliseconds. There was no systematic variation iron concentration throughout the heart, but higher iron levels were found in the epicardium than in the endocardium. The data also show that cardiovascular magnetic resonance measurements in the midventricular septum are very representative of whole-heart iron concentration, which validates the current clinical approach in wide-
spread use. These data show that T2* cardiovascular magnetic resonance 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 transfusion-dependent patients worldwide.

Conclusions: These data detail the iron distribution throughout the heart in iron overload and provide calibration in humans for cardiovascular magnetic resonance T2* against myocardial iron concentration. The iron values are of considerable interest in terms of the level of cardiac iron associated with iron-related death and indicate that the heart is more sensitive to iron loading than the liver. The results also validate the current clinical practice of monitoring cardiac iron in vivo by cardiovascular magnetic resonance of the midseptum.15

Role of Pyruvate Dehydrogenase Inhibition in the Development of Hypertrophy in the Hyperthyroid Rat Heart: A Combined Magnetic Resonance Imaging and Hyperpolarized Magnetic Resonance Spectroscopy Study

Summary: The primary clinical significance of this article lies in the importance of gaining a better understanding of the underlying mechanisms resulting from hyperthyroidism. Using both noninvasive and novel techniques, the authors have thoroughly characterized the relationship between the metabolic and functional consequences of hyperthyroidism. By studying the metabolic perturbations associated with hyperthyroidism and using this information to devise a treatment regimen to improve metabolic flexibility in the hyperthyroid heart, the authors have uniquely shown that the associated cardiac hypertrophy can be reduced. The authors have also found that under conditions of plentiful energy supply, the heart is able to alter its response to maintain cardiac output. These findings are undoubtedly important, not only for this disease but also for other metabolic diseases affecting the heart. Furthermore, the potential to study the metabolic effects of hyperthyroidism and other cardiovascular diseases in humans with the hyperpolarized techniques presented here is clear. The first trials in humans with hyperpolarized pyruvate as a metabolic biomarker are imminent and offer many advantages over other forms of metabolic assessment such as including no radiation exposure and being a minimally invasive procedure. Metabolic studies with this technology can be integrated into existing MRI assessments of cardiac structure and function, as demonstrated here with a combined cine MRI and hyperpolarized magnetic resonance spectroscopy assessment.

Conclusions: This work has demonstrated that inhibition of glucose oxidation in the hyperthyroid heart in vivo is mediated by pyruvate dehydrogenase kinase. Relieving this inhibition can increase the metabolic flexibility of the hyperthyroid heart and reduce the level of hypertrophy that develops while maintaining the increased cardiac output required to meet the higher systemic metabolic demand.16

Role of Cardiovascular Magnetic Resonance 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, for example, 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 enhanced 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 ascribed by 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%), and the data suggest 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 as 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 just 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.17

Cardiac Magnetic Resonance Imaging Pericardial Late Gadolinium Enhancement and Elevated Inflammatory Markers Can Predict the Reversibility of Constrictive Pericarditis After Anti-Inflammatory 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 anti-inflammatory therapy have been described, but there is no known method to predict the reversibility. The authors report their pilot study to assess whether cardiac MRI (CMR) pericardial late gadolinium enhancement (LGE) can predict the reversibility of CP after a course of anti-inflammatory therapy. Twenty-nine patients received anti-inflammatory medications after CMR. Fourteen patients 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 and erythrocyte sedimentation rate level than the persistent CP group. Anti-inflammatory therapy was associated with a reduction in pericardial LGE, C-reactive protein, and erythrocyte sedimentation rate level in the reversible CP group but not in the persistent CP group. The authors’ findings in this pilot observation suggest that reversible CP is associated with pericardial and systemic inflammation. Furthermore, anti-inflammatory therapy is associated with a reduction of pericardial and systemic inflammation, as well as pericardial thickness on CMR LGE imaging, with resolution of constrictive physiology and symptoms. Anti-inflammatory therapy should be considered in CP patients with these features before pericardiectomy. The findings must be validated by further studies in a larger number of patients.

Conclusions: Reversible CP was associated with pericardial and systemic inflammation. Anti-inflammatory therapy was associated with a reduction in pericardial LGE, C-reactive protein, and erythrocyte sedimentation rate level in the reversible CP group. The authors’ findings in this pilot observation suggest that reversible CP is associated with pericardial and systemic inflammation. Furthermore, anti-inflammatory therapy is associated with a reduction of pericardial and systemic inflammation, as well as pericardial thickness on CMR LGE imaging, with resolution of constrictive physiology and symptoms. Anti-inflammatory therapy should be considered in CP patients with these features before pericardiectomy. The findings must be validated by further studies in a larger number of patients.

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: discontinuous conduction curves, dual pathway atrioventricular conduction, autonomic modulation of the AV junctional pacemaker site, and so forth. 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 present 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 present evidence of fast- and slow-pathway AVN conduction. Second, the authors present evidence of autonomic modulation of the AVN pacemaker. Third, the authors present evidence of longitudinal dissociation during AV functional rhythm, indicating the existence of a functional barrier between the 2 compartments in the human AVN and its extensions, which the authors have 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 open a possibility for future application of optical mapping in the clinical electrophysiology laboratory.

Conclusions: The authors have demonstrated that the AVJ pacemaker in failing human hearts is located in the nodal-His region or His bundle regions and can be modified with autonomic stimulation. Moreover, we found that both the fast and slow pathways are involved in anterograde and retrograde conduction.19

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 propose a 4-tiered classification based on whether or not LV concentricity0.67 is increased. LVH is concentric; otherwise the LVH is eccentric. The authors propose a 4-tiered classification based on whether or not LV concentricity0.67 is increased. LVH is concentric; otherwise the LVH is eccentric. The authors propose a 4-tiered classification based on whether or not LV concentricity0.67 but not LVEDV (“thick hypertrophy”), 53 had increased LVEDV and no increase in troponin T or natriuretic peptide levels versus those with dilated hypertrophy. 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.21

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 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 to 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 >–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.21

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 the current study, the prognostic value of RV function in 612 consecutive patients admitted with AMI treated with primary percutaneous coronary intervention, 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, reinfection, and hospitalization for heart failure. RV fractional area change (hazard ratio, 0.96; 95% confidence interval, 0.92–0.99) and RV strain (hazard ratio, 1.08; 95% confidence interval, 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. In conclusion, RV function provides useful prognostic information in patients treated with primary percutaneous coronary intervention for AMI.

Conclusions: RV function provides strong prognostic information in patients treated with primary percutaneous coronary intervention for AMI.21

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

Summary: Despite excellent results regarding 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, underscoring 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 anterosetal 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, 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.

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

Summary: This article explores the utility of a new MRI method for identifying subclinical cardiotoxicity caused by doxorubicin chemotherapy. At present, surveillance strategies for doxorubicin cardiotoxicity involve serial assessments of left ventricular ejection fraction 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. In this article, the authors describe a new MRI method that identified abnormal myocardial tissue characteristics early after doxorubicin exposure and before marked changes in left ventricular ejection fraction. Moreover, an absence of change in MRI tissue characteristics predicted preserved left ventricular ejection fraction 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 left ventricular ejection fraction have occurred.

Conclusions: After doxorubicin, low serial measures of Gd-SI predict an absence of left ventricular ejection fraction drop or unanticipated death. An increase in Gd-SI after doxorubicin forecasts a subsequent drop in left ventricular ejection fraction as well as histopathologic evidence of intracellular vacuolization consistent with doxorubicin cardiotoxicity.

Pulmonary Vascular Resistance, Collateral Flow, and Ventricular Function in Patients With a Fontan Circulation at Rest and During Dobutamine Stress

Summary: The pathophysiologic causes for failure of the Fontan circulation are multifactorial. Therefore, diagnostic tools are warranted that permit a differential analysis of ventricular and pulmonary vascular function. In this study, an MRI catheterization technique that enables simultaneous pressure and volume measurement in the single ventricle was used. From these measurements, parameters of global pump, myocontractile, and diastolic function can be derived. In addition, MRI catheterization allows determination of aortopulmonary collateral flow in conjunction with pulmonary vascular resistance. The authors found that pharmacological stress by dobutamine improved contractility, although without substantial augmentation of stroke volumes. At the same time, the single ventricle showed signs of abnormal diastolic performance. In the absence of a subpulmonary ventricle, these findings should be seen in the light of pulmonary vascular function. In the studied patients, blood flow through aortopulmonary collaterals contributed substantially to the total pulmonary blood flow. In addition, its proportion increased during stress. However, augmented total pulmonary blood flow was not associated with increased pulmonary vascular resistance, implying that resistance did not contribute to a limited preload reserve and thus impaired diastolic filling of the systemic ventricle. The method described in this study provides detailed and differential information of the cardiovascular function in Fontan, which will potentially improve the planning of individual treatment strategies. The findings of this descriptive study of preselected patients require further study in larger groups of patients with different types of Fontan circulation.

Conclusions: In patients with a Fontan circulation, aortopulmonary collateral flow contributes substantially to enhanced pulmonary flow during stress. The data indicate that pulmonary vascular response to augmented cardiac output was adequate, but decreased diastolic compliance was identified as an important component of ventricular dysfunction.

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 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.

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. 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 magnetic resonance
spectroscopy methods were adapted 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, increasingly used to probe molecular mechanisms of human disease and contractile function in the same examination. Murine models are powerful means to assess cardiac energy metabolism, structure, mass, and contractile function in the same examination and be repeated over time as pathology develops. The observations demonstrate 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 the small size and high murine heart rate, the ATP synthesis rate through creatine kinase is similar in vivo in murine and human hearts and comparably reduced in heart failure 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.27

**Relation Between Right Ventricular Function and Increased Right Ventricular**

$[^{18}F]$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 right ventricle may serve as a potential target for the management of RV failure. This study was designed to characterize myocardial metabolism in the right ventricle 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 $[^{18}F]$fluorodeoxyglucose uptake, the magnitude of which may be correlated with severity.28

**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 increase in New York Heart Association class) during a median follow-up of 17 months was examined in 343 diabetic and 618 nondiabetic subjects with New York Heart Association class II or III heart failure 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, 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 class. 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 diabetic subjects. Conversely, there was no difference in the risk of HF progression between diabetic and nondiabetic 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, treatments designed to prevent or ameliorate cardiac sympathetic denervation in diabetic subjects (eg, $\beta$-adrenergic–blocking drugs) may provide additional benefit for prevention of HF progression beyond those therapies focused primarily on treatment of diabetes.

**Conclusions:** The combination of diabetes mellitus and I-123 metaiodobenzylguanidine H/M ratio is an independent predictor of heart failure progression, confirming the high risk of diabetic subjects with impaired cardiac sympathetic nerve function.29

**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 estimation of 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, 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 identifying patients with increased wedge pressure. In 12 repeat studies, Doppler echocardiography readily detected the changes in mean wedge pressure as well as other hemodynamic changes.

**Conclusions:** Doppler echocardiography provides reliable assessment of right and left ventricular hemodynamics in patients with decompensated heart failure.30

**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. This study provides evidence that LGE-CMR is a reliable diagnostic tool to confirm EMF.

**Conclusions:** This 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.31

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

**Summary:** Cardiac magnetic resonance (CMR) can provide a wide range of prognostic information in acute ST-elevation myocardial infarction (STEMI) 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 intramyocardial hemorrhage. However, the clinical signifi-
cance of such findings has not yet been established. The present study is 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 AAR of reperfused infarcted myocardium in T2-weighted CMR is a frequent finding in reperfused STEMI patients 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 IMH, 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 in T2-weighted CMR is closely related to infarct size, microvascular obstruction, and impaired left ventricular function, with subsequent adverse clinical outcome.32

**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, tissue Doppler, and color M-mode have shown promise in the estimation of left-sided filling pressures. Two such indices, E/e' and E/Vp, have received recognition for their utility in the 1-time estimation of left-sided filling pressures in healthy subjects as well as 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 within individuals as filling pressures vary. To test this hypothesis, the authors made multiple, simultaneous measures of E/e', E/Vp, and pulmonary capillary wedge pressure within healthy subjects and patients with heart failure with preserved ejection fraction 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 techniques in research studies with healthy volunteers or to titrate medical therapy in patients with heart failure with preserved ejection fraction.

**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 heart failure with preserved ejection fraction.33

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

**Summary:** Cardiac 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 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 hypoenhanced tissue on delayed-enhancement 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 hypoenhanced tissue. In multivariable analysis, age, LVEF, and number of segments with hypoenhanced tissue were independent predictors of mortality. The number of segments with hypoenhanced tissue provided incremental prognostic value beyond clinical data and LVEF. Even in patients with near-normal LVEF, significant damage identifies 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.34

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

**Summary:** The development of diffuse myocardial fibrosis 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 diffuse myocardial fibrosis 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 diffuse myocardial fibrosis 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 diffuse myocardial fibrosis by quantification of myocardial ECV.35

**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 (New York Heart Association functional class III). 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 15N-NH3 and 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 pulmonary arterial hypertension. In addition, the study demonstrates 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 pulmonary arterial hypertension. Monitoring myocardial glucose uptake level may help to optimize treatment to improve function and outcome.

Conclusions: PET scanning with 13N-NH3 and 18F-fluorodeoxyglucose is a feasible modality for quantifying RV blood flow and metabolism in patients with idiopathic pulmonary arterial hypertension.

Echocardiographic Variables After LVAD 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 left ventricle and atrium and those assessing right ventricular function. The only right ventricular variable significantly associated with adverse outcome was a decreased tissue Doppler velocity of the lateral tricuspid annulus. The variables assessing LV unloading associated with adverse outcome were a high estimated left atrial pressure (>15 mm Hg) and a short mitral inflow deceleration time divided by the E-wave velocity (<2 ms/cm/s). An interventricular septum deviated to the left was associated with worse outcome as well. In conclusion, echocardiographic variables suggestive of efficient but not excessive LV unloading are associated with favorable mid- and long-term outcome after LVAD surgery.

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

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 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 percutaneous coronary intervention, 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 article demonstrates a decrease in infarct size of 18% with ischemic postconditioning. Being the first to evaluate effect of ischemic postconditioning by cardiac magnetic resonance, the authors believe 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 percutaneous coronary intervention. The impact of mechanical postconditioning seems to be independent of the size of myocardium at risk.

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 outliers are the least likely to undergo testing.

Conclusions: Nearly 40% of Medicare beneficiaries do not undergo assessment of left ventricular function when newly diagnosed with heart failure. Quality-improvement strategies are needed to optimize the care of these patients, especially in outpatient settings.

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