Long-Term Recording of Cardiac Arrhythmias With an Implantable Cardiac Monitor in Patients With Reduced Ejection Fraction After Acute Myocardial Infarction: The Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) Study

Summary: Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) reports on long-term cardiac arrhythmias recorded by an implantable cardiac monitor in patients with left ventricular ejection fraction ≤40% after myocardial infarction. Clinically significant bradycardias and tachyarrhythmias were documented in a substantial proportion of patients, most of them asymptomatic. A large number of the documented arrhythmias would result in device therapy according to the current guidelines. The most significant arrhythmia was intermittent high-degree atrioventricular block, which was associated with a very high risk of cardiac death. However, the study was observational, and whether the use of implantable cardiac monitors in this population could improve clinical outcome should be tested in larger randomized trials.

Conclusions: This is the first study to report on long-term cardiac arrhythmias recorded by an implantable loop recorder in patients with left ventricular ejection fraction ≤40% after myocardial infarction. Clinically significant bradycardias and tachyarrhythmias were documented in a substantial proportion of patients with depressed left ventricular ejection fraction after acute myocardial infarction. Intermittent high-degree atrioventricular block was associated with a very high risk of cardiac death.

Effect of Long-Term Right Ventricular Pacing in Young Adults With Structurally Normal Heart

Summary: This study elucidates the long-term effect of right ventricular (RV) pacing on clinical outcomes in patients who underwent pacemaker implantation for symptomatic isolated congenital complete atrioventricular block (ICAVB). Over a mean follow-up of 20 years (longest, 39 years), the observed survival free of new heart failure (HF) after pacemaker implant in the overall ICAVB group was significantly worse than that of the age- and sex-specific Olmsted County, Minnesota, population rates. This difference was, however, attributable to the development of HF and ventricular dysfunction in those who had tested positive for antinuclear antibody (ANA) during adulthood, with no difference between the antibody negative ICAVB patients and the Olmsted County population. The presence of a positive ANA was a strong predictor for the development of HF and death. These results suggest that in young patients without structural heart disease, pacing from the RV position does not appear to have a detrimental effect on heart size or performance. The risk of HF after pacemaker implant is not solely the result of abnormal ventricular activation, but instead an interaction between pacing and abnormal myocardial substrate. In ICAVB patients, positive antibody status may predispose to cardiomyopathy and worse clinical outcomes. ANA testing should supplement the assessment of ventricular size and function by echocardiography to identify high-risk patients who might progress to HF.

Conclusions: The natural history of patients with isolated congenital atrioventricular block who require pacing depends on their antibody status. ANA status was a predictor for the development of HF and death. Long-term RV pacing alone does not appear to be associated with development of heart failure, deterioration in ventricular function, or reduced survival in Ab− isolated congenital atrioventricular block patients.

Role of RBM25/LUC7L3 in Abnormal Cardiac Sodium Channel Splicing Regulation in Human Heart Failure

Summary: The authors have previously shown that human heart failure is associated with abnormal mRNA splicing of the cardiac sodium channel. This abnormal mRNA splicing results in truncated sodium channels that are nonfunctional and a reduction in sodium channel current to levels known to cause sudden death. The authors explored the mechanisms by which this abnormal splicing occurs. Using microarray comparisons of diseased and normal human hearts, they identified 2 splicing factors, RBM25 and LUC7L3, which were necessary and sufficient to cause the abnormal sodium channel splicing. These factors were upregulated by hypoxia and elevated angiotensin II, conditions known to be present in heart failure. Moreover, the authors showed that the responses of white cells and heart to these 2 inciting stimuli were equivalent. The potential clinical implications of these findings include a possible mechanism whereby hypoxia is arrhythmogenic and blockade of the renin-angiotensin system is antiarrhythmic. Moreover, if white cell sodium channel splicing in vivo correlates with that in the myocardium, it may be possible to develop a blood test to assess sodium channel availability and arrhythmic proclivity. Finally, this work defines potential therapeutic targets to address arrhythmic risk in human heart failure.

Correspondence to The Editors, Circulation: Heart Failure Editorial Office, 560 Harrison Ave, Suite 502, Boston, MA 02118. E-mail circ@circulationjournal.org
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Conclusions: Of the 17 mRNA splicing factors upregulated in heart failure, RBM25 and LUC7L3 were sufficient to explain the increase in truncated forms and the reduction in full-length Na^+ channel transcript. Because the reduction in channels was in the range known to be associated with sudden death, interruption of this abnormal mRNA processing may reduce arrhythmic risk in heart failure.3

Primary Results From the SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy (SMART-AV) Trial: A Randomized Trial Comparing Empirical, Echocardiography-Guided, and Algorithmic Atrioventricular Delay Programming in Cardiac Resynchronization Therapy

Summary: The clinical benefit of cardiac resynchronization therapy for patients with moderate to severe symptomatic heart failure, severe left ventricular systolic dysfunction, and intraventricular conduction delay is firmly established. Nonetheless, a significant number of patients derive limited benefit from cardiac resynchronization therapy. One possibility is that systematic optimization of the programmed atrioventricular (AV) delay might improve overall outcomes. A variety of methods are used clinically for programming the AV delay, with no current consensus on the best practice. The SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy (SMART-AV) delay trial prospectively randomized patients to a fixed empirical AV delay (120 ms), echocardiographically optimized AV delay, or AV delay optimized with SmartDelay, an empirically derived electrogram-based algorithm. A total of 980 patients were randomized and followed up for 6 months. At the end of the trial, there was no difference in the primary end point, left ventricular end-systolic volume, or any of the secondary end points: left ventricular end-diastolic volume, ejection fraction, New York Heart Association class, quality of life, and 6-minute walk distance. The routine use of echocardiographic optimization and algorithm-based AV interval optimization is not clinically warranted. However, these data do not exclude possible utility in selected patients who do not respond to cardiac resynchronization therapy.

Conclusions: Neither SmartDelay nor echocardiography was superior to a fixed AV delay of 120 ms. The routine use of AV optimization techniques assessed in this trial is not warranted. However, these data do not exclude possible utility in selected patients who do not respond to cardiac resynchronization therapy.4

SERCA2a Gene Transfer Decreases Sarcoplasmic Reticulum Calcium Leak and Reduces Ventricular Arrhythmias in a Model of Chronic Heart Failure

Summary: Systolic and diastolic function in heart failure is strongly linked to decrease of calcium ion uptake into the sarcoplasmic reticulum (SR) secondary to the loss of SR calcium ATPase 2a (SERCA2a). SERCA2a gene therapy is an encouraging new therapeutic strategy, and, in contrast to other positive inotropes, it imparts these benefits in an energetically favorable manner. However, there is concern that SERCA2a upregulation might be proarrhythmic in the same way as catecholamine-related inotropes. In the present study, the authors assessed the arrhythmic effects of SERCA2a gene transfer in a rat model of chronic heart failure after myocardial infarction. In vivo telemetry studies demonstrated a reduction in spontaneous, and perhaps more importantly, catecholamine-induced ventricular arrhythmias after SERCA2a gene therapy. Programmed electric stimulation studies showed reduced susceptibility to S1–S2–induced ventricular tachycardia. Leak from the internal calcium reservoir, the SR, when measured as either spontaneous “diastolic” calcium sparks, or total SR calcium leak, was reduced after SERCA2a gene therapy. SR calcium leak is a potential origin of delayed afterdepolarizations and ventricular tachyarrhythmias, and catecholamine-induced triggered activity was reduced in failing cardiomyocytes after SERCA2a gene therapy. Both direct effects of restored SERCA2a protein levels and the indirect effects of reverse remodeling secondary to improved cardiac function may underpin the antiarrhythmic effects observed. SERCA2a gene therapy represents a novel class of heart failure therapy in which positive inotropic and lusitropic benefits can be achieved with a concomitant antiarrhythmic effect in this animal heart failure model.

Conclusions: SERCA2a gene therapy stabilizes SR Ca^{2+} load, reduces ryanodine receptor phosphorylation and decreases SR Ca^{2+} leak, and reduces cellular triggered activity in vitro and spontaneous and catecholamine-induced ventricular arrhythmias in vivo in failing hearts. SERCA2a gene therapy did not therefore predispose to arrhythmias and may represent a novel antiarrhythmic strategy in heart failure.5

Autonomic Remodeling in the Left Atrium and Pulmonary Veins in Heart Failure: Creation of a Dynamic Substrate for Atrial Fibrillation

Summary: Atrial fibrillation (AF) is common in patients with heart failure. Although atrial fibrosis is a likely factor, other factors probably are important as well. This study suggests that the autonomic nervous system also contributes significantly to the formation of AF substrate in a canine model of heart failure. The authors found that unlike the failing ventricle, where there appears to be parasympathetic withdrawal, there is an increase in parasympathetic innervation in the failing atrium, which appears to contribute to the maintenance of AF. They also show that both sympathetic and parasympathetic remodeling occur and are most pronounced in the posterior left atrium. These findings support further evaluation of ablation of autonomic ganglionated plexi to improve the success AF ablation in heart failure. The data also support exploration of the parasympathetic nervous system as a therapeutic target for prevention of AF in the failing heart.

Conclusions: In this heart failure model, autonomic and electrophysiological remodeling occurs, involving the posterior left atrium and pulmonary veins. Despite synaptic compensation, parasympathetic hyperinnervation contributes significantly to AF maintenance. Parasympathetic and/or sympathetic signaling may be possible therapeutic targets for AF in congestive heart failure.6

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

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

**Conclusions:** Elevated atrial ET-1 content is associated with increased LA size, AF rhythm, hypertension, and heart failure. ET-1 is associated with atrial dilatation, fibrosis, and hypertrophy and probably contributes to AF persistence. Interventions that reduce atrial ET-1 expression and/or block its receptors may slow AF progression.

### Success of Ablation for Atrial Fibrillation in Isolated Left Ventricular Diastolic Dysfunction: A Comparison to Systolic Dysfunction and Normal Ventricular Function

**Summary:** Although ablation of atrial fibrillation has been followed by an improvement in left ventricular (LV) ejection fraction in selected patients with LV systolic dysfunction, there are concerns that ablation procedures in patients with heart failure have the potential for greater risk, less efficacy, and limited impact on quality of life. For patients with isolated diastolic dysfunction, these issues are also unclear. This investigation compared outcomes after catheter ablation in patients with depressed LV ejection fraction, preserved LV ejection fraction with diastolic dysfunction, and normal systolic and diastolic function. At 1 year, the atrial fibrillation elimination rate of 75% in patients with isolated LV diastolic dysfunction was comparable to that in patients with normal LV function and was better than that in patients with LV systolic dysfunction (62%). All 3 groups experienced improvement in physical and mental quality of life. LV ejection fraction improved to near normal in 31% of the LV dysfunction group. In the diastolic dysfunction group, 30% of patients showed improvement in diastolic dysfunction. Over 5 years, there were more atrial fibrillation recurrences in the LV systolic and diastolic dysfunction groups than in the normal group. Therefore, repeat ablation or supplemental antiarrhythmic therapy may be required more often in the long-term management of atrial fibrillation in populations with LV dysfunction.

**Conclusions:** Although an ablative approach for atrial fibrillation in patients with systolic or diastolic dysfunction is associated with an increased long-term recurrence risk, there is potential for substantial quality-of-life improvement and LV functional benefit.

### Calcium-Calmodulin Kinase II Mediates Digitalis-Induced Arrythmias

**Summary:** Cardiac glycosides have been used for the treatment of congestive heart failure for more than 200 years; however, these compounds have a narrow therapeutic window because of the presence of adverse toxic effects, including arrhythmias, which limit their extensive use in the clinical practice. The arrhythmic effects have been proposed to occur when sarcoplasmic reticulum (SR) Ca²⁺ storage capacity is exceeded and spontaneous SR Ca²⁺ release (Ca²⁺ waves) arise and activate a depolarizing current, which, if sufficiently large, may achieve threshold and generate spontaneous action potentials and ventricular arrhythmias. In the present study, the authors show that cardiac glycoside activates calcium-calmodulin kinase II (CaMKII), which phosphorylates the ryanodine receptor-favoring spontaneous SR Ca²⁺ release, predisposing the heart for delayed afterdepolarization-triggered arrhythmias. The results also reveal that CaMKII inhibition prevents digitalis-induced arrhythmias without affecting its positive inotropic effect, suggesting the potential use of CaMKII inhibitors as an adjunct to digitalis for the treatment of heart failure. Thus, the authors’ findings could not only help to widen the therapeutic window of cardiac glycosides but also help to explain the enhanced propensity for fatal arrhythmias observed in heart failure patients, where high levels of endogenous ouabain-like compounds and CaMKII expression have been reported.

**Conclusions:** These results show for the first time that CaMKII mediates ouabain-induced arrhythmic/toxic effects. The authors suggest that CaMKII-dependent phosphorylation of the ryanodine receptor, resulting in Ca²⁺ leak from the SR, is the underlying mechanism involved.

### Anatomic Localization and Autonomic Modulation of Atrioventricular Functional 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, they present evidence of fast- and slow-pathway AVN conduction. Second, they present evidence of autonomic modulation of the AVN pacemaker. Third, they present 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 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 AV junctional 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 antegrade and retrograde conduction.

### Myocardial Infarction Does Not Preclude Electric and Hemodynamic Benefits of Cardiac Resynchronization Therapy in Dyssynchronous Canine Hearts

**Summary:** The main findings of this study in the novel canine model of left bundle-branch block combined with myocardial infarction indicate that infarcted hearts as well as noninfarcted hearts with left bundle-branch block can benefit from cardiac resynchronization therapy. Achieving the maximal benefit in infarcted hearts, however, requires accurate positioning of the left ventricular (LV) pacing lead and more precise timing of LV stimulation. The presence and location of the infarction determines the best pacing site. This best site does not coincide with the region of latest activation but can be recognized as the site providing the most profound reduction in QRS duration.

**Conclusions:** Cardiac resynchronization therapy can improve resynchronization and LV pump function to a similar degree in infarcted and noninfarcted hearts. Optimal lead positioning and timing of LV stimulation, however, require more attention in the infarcted hearts.
Effect of Right Ventricular Versus Biventricular Pacing on Electric Remodeling in the Normal Heart

Summary: Biventricular pacing (BiV) has been shown to have beneficial effects in a subset of patients with systolic heart failure and to prevent the deleterious effects of high-burden right ventricular (RV) pacing in patients with preserved left ventricular function. The mechanisms of these salutary effects are not fully elucidated. In this study, the authors examined the effect of BiV versus RV pacing on the normal heart in a rabbit model of epicardial pacing. After 4 weeks of pacing, the QT interval was significantly shorter in the BiV group compared with the RV or sham-operated (nonpaced) groups. Also, compared with rabbits in the RV group, rabbits in the BiV group had shorter RV effective refractory period and shorter left ventricular paced QT interval during the drive train of stimuli and close to refractoriness. Also, protein expression of the KVLQT1 was significantly increased in the BIV group compared with the RV and control groups, whereas protein expression of SCN5A and connexin43 was significantly decreased in the RV compared with the other study groups. Erg protein expression was significantly increased in both pacing groups compared with the controls.

Conclusions: In this rabbit model, the authors demonstrate a direct effect of BiV but not RV pacing on shortening the native QT interval as well as the paced QT interval during burst pacing and close to the ventricular effective refractory period. These findings underscore the fact that the effect of BiV pacing is partially mediated through direct electric remodeling and may have implications as to the effect of BiV pacing on arrhythmia incidence and burden.12

Paced Left Ventricular QRS Width and ECG Parameters Predict Outcomes After Cardiac Resynchronization Therapy: PROSPECT-ECG Substudy

Summary: In this PROSPECT-ECG substudy, only QRS left bundle-branch block (LBBB) morphological features were predictive of both left ventricular end-systolic volume (LVESV) and clinical composite score (CCS) response; other ECG parameters were predictive of one or the other. Both parameters that predicted either LVESV or CCS response (namely, LV-paced QRS width and the difference between biventricular [Bi-V] and preimplantation QRS width) can be measured intraprocedurally and can be used by the cardiac resynchronization therapy (CRT) implantator to optimize LV lead placement or pacing. To improve CRT response, as measured by CCS or LVESV, the data suggest selecting only patients with baseline LBBB. In addition, during CRT implantation, particularly in patients with nonischemic cardiomyopathy, it is recommended that the LV lead be positioned to minimize both the LV-paced QRS and the Bi-V-paced QRS widths, especially if there are multiple coronary veins, multiple locations within a vein, or multiple pacing configurations from which to choose.

Conclusions: Baseline left bundle-branch QRS morphological features, LV-paced QRS width, and the difference between Bi-V and preimplantation QRS width can predict positive outcomes after CRT and may represent a novel intraprocedural method to optimize coronary sinus lead placement.13

Long-Term Outcome After Ablative Therapy of Postoperative Atrial Tachyarrhythmia in Patients With Congenital Heart Disease and Characteristics of Atrial Tachyarrhythmia Recurrences

Summary: Catheter ablation of atrial tachyarrhythmias in patients with congenital heart disease can be challenging, and long-term outcome data are limited. The authors examined atrial tachyarrhythmias in 53 patients (median age, 35 years) who underwent catheter ablation for atrial arrhythmias after surgery for congenital heart disease. Mac rotor ventricular arrhythmias were most common, but focal tachycardias also occurred. During a follow-up period of 5±3 years, tachyarrhythmias recurred in 29 patients but were often different from the previously ablated tachycardias. Persistent atrial fibrillation developed in 14 patients. Despite the frequent need for repeat ablation, most patients are in sinus rhythm.

Conclusions: Successful postoperative atrial tachyarrhythmia in congenital heart disease patients developing over time may be caused by different mechanisms, including focal and reentrant mechanisms. Recurrent atrial tachyarrhythmia originated from different locations, suggesting that these new atrial tachyarrhythmias were not caused by arrhythmogenicity of previous ablatve lesions. Long-term outcome is often complicated by development of atrial fibrillation.14

Surgical Ablation of Refractory Ventricular Tachycardia in Patients With Nonischemic Cardiomyopathy

Summary: Catheter ablation is an important option to control recurrent ventricular tachycardia (VT). Success rates continue to improve as our understanding of VT physiology is growing and better ablation tools are introduced. However, some VT circuits are still inaccessible to percutaneous ablation. In the majority of these cases, the VT circuit involves a midmyocardial scar, which precludes effective energy delivery or is in close proximity to an epicardial coronary vessel, limiting the ability to intervene. In these patients, surgical ablation is an alternative approach. This study shows that surgical ablation guided by preoperative electroanatomic and electrophysiological mapping can be effective. Therefore, when these VTs are encountered, surgical ablation should be considered.

Conclusions: VT circuits inaccessible to percutaneous ablation techniques are rare but can be encountered in patients with nonischemic cardiomyopathy. These VTs can be successfully targeted by surgical cryoablation guided by preoperative electroanatomic and electrophysiological mapping.15

Left Ventricular Systolic Dysfunction Induced by Ventricular Ectopy: A Novel Model for Premature Ventricular Contraction-Induced Cardiomyopathy

Summary: Premature ventricular contractions (PVCs) are a common entity associated with cardiomyopathy and other cardiac diseases, and yet their effects on the cardiovascular system are not well understood. This is primarily because of the lack of animal models and the unpredictability and variability of PVCs in the clinical setting. With the use of a novel premature pacing algorithm capable of reproducing different clinical scenarios of ventricular ectopy, the effects of chronic ventricular bigeminy in structurally normal hearts were studied in an animal model. The authors’ canine model validates and describes for the first time the time course of echocardiographic findings, changes in ventricular effective refractory period, and the histopathologic and mitochondrial characteristics of PVC-induced cardiomyopathy. These findings support further clinical studies in patients with cardiomyopathy associated with frequent PVCs because the minimum PVC burden, origin, and coupling interval required to induce cardiomyopathy remain unclear. Finally, this novel premature pacing algorithm and PVC animal model will facilitate further scientific evaluation of the cardiovascular effects of PVCs in structurally normal hearts and other established heart failure models.

Conclusions: This novel PVC animal model demonstrates that frequent PVCs alone can induce a reversible form of cardiomyopathy in otherwise structurally normal hearts. PVC-induced cardiomyopathy lacks gross histopathologic and mitochondrial abnormalities seen in other canine models of cardiomyopathy.16
A ZASP Missense Mutation, S196L, Leads to Cytoskeletal and Electric Abnormalities in a Mouse Model of Cardiomyopathy

Summary: Dilated cardiomyopathies are often genetic and associated with arrhythmias and sudden cardiac death. The links between genetic mutations causing dilated cardiomyopathy and arrhythmias are not well defined. The authors studied a mouse model for the S196L mutation in the cytoskeletal protein ZASP previously identified in a family with dilated cardiomyopathy and sudden cardiac death. Affected mice have evidence of digital abnormalities at 3 months of age and develop hemodynamic impairment and rhythm disturbances by 10 months of age. In isolated cells, the ZASP-S196L mutation was found to affect L-type Ca\textsuperscript{2+} currents and Na\textsuperscript{+} currents. Furthermore, ZASP can form a protein complex including both calcium (Ca\textsubscript{1.2}) and sodium (Na\textsubscript{1.5}) channels and the ZASP-binding partners Z-disk proteins α-actinin-2 and Telethonin. These findings suggest that primary mutations in any of the components of such complexes could lead to disturbances in the intertwined connection between the cytoskeleton and ion channels, suggesting a group of potentially novel causes of cardiomyopathies associated with arrhythmias.

Conclusions: The findings provide new insight into the mechanisms by which mutations of a structural/cytoskeletal protein, such as ZASP, lead to cardiac functional and electric abnormalities. This work represents a novel framework to understand the development of conduction defects and arrhythmias in subjects with cardiomyopathies, including dilated cardiomyopathy.

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 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, which 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 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.

Cardiac Sympathetic Reserve and Response to Cardiac Resynchronization Therapy

Summary: Heart failure is associated with deregulated 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 (\textsuperscript{123}I-MIBG) heart/mediastinum ratio and attenuated heart/mediastinum washout rate, determined by \textsuperscript{123}I-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 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 perspective, reversible sympathetic inhibition determined by \textsuperscript{123}I-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.

The S1103Y Cardiac Sodium Channel Variant Is Associated With Implantable Cardioverter-Defibrillator Events in Blacks With Heart Failure and Reduced Ejection Fraction

Summary: Sudden cardiac death (SCD) risk stratification for primary prevention implantable cardioverter-defibrillators (ICDs) is currently limited to reduced ejection fraction, yet the majority of people having SCD do not meet the criteria, nor do the majority of patients receiving primary prevention ICDs derive benefit from the device. In this report, the authors show that the S1103Y variant in the cardiac sodium channel gene, present in approximately 13% of blacks, is associated with a 3- to 4-fold increase in ICD “events” in patients with reduced ejection fraction. This genetic association is independent of traditional clinical risk factors for SCD. Identifying patients with this variant may potentially improve risk stratification for SCD in blacks, in whom there is a high prevalence of this variant.

Conclusions: This is the first report that the S1103Y variant is associated with a higher incidence of ventricular arrhythmias in blacks with heart failure and reduced ejection fraction.

Modulation of Mitochondrial Proteome and Improved Mitochondrial Function by Biventricular Pacing of Dyssynchronous Failing Hearts

Summary: One of the limitations of cardiac resynchronization therapy is that 20% to 30% of the patients demonstrate little clinical benefit, if any at all. The authors believe that insight regarding the molecular mechanisms that are activated by cardiac resynchronization therapy may provide candidate targets that identify responders to this therapy and that proteomics could help in pinpointing the key proteins in this process and could narrow down the search for pathways that are dysregulated in nonresponders. Additionally, the study explores what the beneficial pathways activated by cardiac resynchronization therapy are in a well-established in vivo model.

Conclusions: Cardiac resynchronization therapy potently affects both the mitochondrial proteome and the performance associated with improved cardiac function.
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 beakling 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 dysynchrony 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 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 and left ventricular pressures by micromanometers. The report concludes that the normal 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 dysynchrony.22

Prevalence of Left Ventricular Regional Dysfunction in Arrhythmogenic Right Ventricular Dysplasia: A Tagged MRI Study

Summary: Arrhythmogenic right ventricular cardiomyopathy or dysplasia (ARVC/D) predominantly affects the right ventricle; however, histological and molecular involvement of the left ventricle (LV) is well documented. Global LV function is usually affected in the advanced stages and is an important determinant for the need for heart transplantation. The authors evaluated regional LV strain in ARVC/D patients without overt LV dysfunction using MRI tagging. Patients with definite ARVC/D showed worse regional LV function compared with control subjects. Regional LV function was also significantly decreased in probable ARVC/D patients compared with control subjects, although right ventricular function was comparable between the groups. Thus, the authors report a high prevalence of regional LV dysfunction in ARVC/D despite preserved global LV function. This is in agreement with the current literature that supports the notion that ARVC/D is a biventricular disease; however, the exact significance of this finding is unclear. It is not known whether LV dysfunction is progressive in these patients, and future long-term studies addressing the prognostic significance of minor LV regional abnormalities are needed.

Conclusions: ARVD is associated with regional LV dysfunction, which appears to parallel degree of RV dysfunction. Further large studies are needed to validate this finding and to better define implications of subclinical segmental LV dysfunction.23

Left Atrial Strain and Strain Rate in Patients With Paroxysmal and Persistent Atrial Fibrillation: Relationship to Left Atrial Structural Remodeling Detected by Delayed-Enhancement MRI

Summary: The underlying substrate for atrial fibrillation (AF) is fibrosis, a marker of structural remodeling. AF leads to progressive structural and functional changes in the left atrium (LA). Delayed-enhancement (DE) MRI has been shown to detect LA fibrosis. With vector velocity imaging, using speckle-tracking technology, quantification of atrial strain throughout the cardiac cycle from gray-scale images is feasible. Strain is an indicator of LA compliance or reservoir function, which is impaired in AF caused by fibrosis. Vector velocity imaging overcomes some of the limitations of Doppler-based strain measurements such as angle dependency and influence by loading conditions. In this study, the authors demonstrated an inverse relationship between LA fibrosis by DE-MRI and LA midlateral strain and strain rate by vector velocity imaging. This relationship was more prominent in patients with persistent compared with paroxysmal AF. Lateral wall strain can be reliably imaged and may be used as a surrogate of LA wall fibrosis by DE-MRI. Interestingly, LA fibrosis and strain were not related to common etiologies for AF such as patient age, hypertension, left ventricular filling pressure, or mitral regurgitation. Regardless of the underlying etiology or the duration of AF, the degree of atrial fibrosis was the main determinant of severity of arrhythmia in this cohort. Noninvasive imaging of LA fibrosis may be helpful in predicting the risk of developing AF, guiding therapeutic strategies, and predicting the outcomes in patients with AF. It may allow us to identify patients earlier in their disease process, before the development of severe or irreversible abnormalities.

Conclusions: LA wall fibrosis by DE-MRI is inversely related to LA strain and strain rate, and these are related to the AF burden. Echocardiographic assessment of LA structural and functional remodeling is quick and feasible and may be helpful in predicting outcomes in AF.24

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.25
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. This 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.

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 pulmonary 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 pulmonary 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, reflecting 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.

Extent of and Reasons for Nonuse of Implantable Cardioverter-Defibrillator Devices in Clinical Practice Among Eligible Patients With Left Ventricular Systolic Dysfunction

Summary: The implantable cardioverter-defibrillator (ICD) has been shown to be effective for both primary and secondary prevention of sudden cardiac death. Analyses of claims and registry data have found underuse and disparate use of ICDs in clinical practice. Through detailed medical record abstraction, the authors found that a majority of heart failure patients who were seemingly eligible for an ICD had a contradiction to the ICD or had refused the ICD. After accounting for true ICD eligibility, the rate of underuse was only 13%. Unlike previous analyses of claims or registry data, we found that after accounting for true ICD eligibility, there was no association between female sex or advanced age and lack of ICD use.

Conclusions: On the basis of a detailed chart review, the true rate of ICD underuse may be substantially lower than previous estimates. In the mechanically dysynchronous 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.
addition, after accounting for ICD eligibility criteria, patient sex and age disparities in ICD therapy were no longer present.29

Underutilization of β-Blockers in Patients Undergoing Implantable Cardioverter-Defibrillator and Cardiac Resynchronization Procedures

Summary: Current guidelines emphasize the need for optimal medical therapy before implantation of cardiac devices (implantable cardioverter-defibrillator, cardiac resynchronization therapy) in patients with heart failure. β-Blockers in particular may decrease the incidence of sudden cardiac death and may lead to clinically important improvements in left ventricular ejection fraction. β-Blockers are underused in the 90 days before cardiac device procedures. There is a modest increase in use after the procedure, but this remains. This highlights the need for strategies geared toward ensuring maximal use of β-blockers in patients undergoing implantation of implantable cardioverter-defibrillators or cardiac resynchronization therapy.

Conclusions: β-Blockers are underused before and after cardiac device procedures. There is a modest increase in use after the procedure. Strategies are required to ensure that patients are on optimal medical therapy before device therapy is selected.30

Elevated B-Type Natriuretic Peptide Is Associated With Increased In-Hospital Mortality or Cardiac Arrest in Patients Undergoing Implantable Cardioverter-Defibrillator Implantation

Summary: Elevated B-type natriuretic peptide (BNP) is associated with increased perioperative mortality. Implantable cardioverter-defibrillator (ICD) implantation is usually well tolerated but occasionally results in death or postimplant cardiac arrest. Markedly elevated BNP before ICD implant is associated with a significantly higher risk of death or cardiac arrest. Preoperative BNP >1000 pg/mL and biventricular ICD implantation is associated with a 2.16% mortality rate in real-world practice. Preimplantation risk assessment should include measurement of BNP.

Conclusions: Elevated BNP level was significantly associated with increased risk of in-hospital mortality or cardiac arrest in patients undergoing ICD implant. Strategies aimed at reducing preprocedural BNP or creating systems to manage procedural risk merit further investigation.31

Improvements in Symptoms and Quality of Life in Patients With Paroxysmal Atrial Fibrillation Treated With Radiofrequency Catheter Ablation Versus Antiarrhythmic Drugs

Summary: For patients with paroxysmal atrial fibrillation (AF) who have failed on 1 or more antiarrhythmic drugs, randomized trials have shown that radiofrequency catheter ablation more successfully maintains sinus rhythm than treatment with a different antiarrhythmic drug. Analysis of symptoms and quality of life (QOL) in prior randomized trials comparing AF ablation and drugs have been limited but tended to suggest better outcomes with ablation. All domains of the Short Form-36, except bodily pain, as well as symptom frequency and severity returned to normal ranges in patients treated with ablation and were significantly better than for patients treated with antiarrhythmic drugs by 3 months after a blanking or dose-titration period. All QOL and symptom measures remained improved in ablation patients until the end of follow-up, whereas no measures convincingly improved in patients who remained on the drugs. In multivariable analysis, the factors most strongly associated with improvement from baseline in all QOL scores were ablation and freedom from recurrent arrhythmia.

Conclusions: For second-line therapy of paroxysmal AF, ablation is superior to antiarrhythmic drug treatment at improving symptoms and QOL.32

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