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Will Imaging Assist in the Selection of Patients With Heart Failure for an ICD?

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Sudden cardiac death remains the leading cause of death in the U.S. A left ventricular ejection fraction (LVEF) <30% to 35% identifies a population of patients at increased risk for sudden cardiac death. Once identified, an implantable cardioverter-defibrillator (ICD) is effective in reducing the occurrence of sudden cardiac death. Yet in a substantial proportion of patients who receive an ICD based on reduced LVEF, the device never delivers therapy. Furthermore, the majority of patients who die suddenly do not qualify for ICD placement under current LVEF-based criteria in the guidelines. This review considers the potential role of cardiac imaging in improving the selection of patients most likely to benefit from an ICD. The presence of myocardial scar and/or unrevascularized myocardial ischemia provides an important substrate for the occurrence of potentially fatal ventricular arrhythmias. The presence of clinical heart failure further increases the risk of ventricular arrhythmia. The sympathetic nervous system provides an important trigger for major arrhythmic events, both through global overactivity and through regional heterogeneity of sympathetic activity. A mismatch of myocardial perfusion and innervation may pose a particularly great risk. Imaging modalities provide unique opportunities to investigate the anatomic and pathophysiologic substrates, as well as the triggering effects of cardiac sympathetic innervation. Combining imaging and electrophysiologic modalities offers promise for improved accuracy in future selection of patients with heart failure for ICD placement. (J Am Coll Cardiol Img 2010;3:101–10) © 2010 by the American College of Cardiology Foundation

Sudden cardiac death (SCD) remains the leading cause of death in the U.S. Unfortunately, success in prospectively identifying individual patients at risk before the occurrence of SCD has been limited. Patients with left ventricular ejection fraction (LVEF) <30% to 35% are at increased risk for SCD, and an implantable cardioverter-defibrillator (ICD) in these patients has been documented to reduce mortality resulting from ventricular arrhythmias (1). Although very helpful, reduced LVEF is a nonspecific predictor of potentially fatal arrhythmic events. In a substantial proportion of patients who receive an ICD based on reduced LVEF, the device never delivers therapy over its lifetime. Furthermore, many patients with LVEF <30% die from progressive heart failure and not SCD. Current American College of Cardiology/American Heart Association guidelines recommend ICD placement for primary prevention of fatal ventricular arrhythmias in patients with New York Heart Association (NYHA) functional class II or III symptoms, while they are undergoing optimal medical treatment, and who have reasonable

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expectation of survival with good functional status for more than 1 year (2). Only approximately one-third of patients who die suddenly have LVEF that meets LVEF-based criteria for prophylactic ICD placement under the current guidelines (3).

A recent scientific statement from the American College of Cardiology/American Heart Association/Heart Rhythm Society reviews numerous electrocardiographic and autonomic reflex-based tests that have been used to identify patients at risk for SCD (4). The statement concludes that the "optimal way to combine and use the techniques in clinical practice remains unclear." With the exception of measurement of LVEF, the scientific statement provides minimal information on the use of imaging techniques for identification of patients at risk for SCD. The present review considers imaging approaches to guide the selection of patients for ICD placement, with specific focus on the arrhythmogenic role of the sympathetic nervous system in a context of myocardial scar and/or ischemia.

ABBREVIATIONS AND ACRONYMS

BNP = B-type natriuretic peptide

CMR = cardiac magnetic resonance

H/M = heart to mediastinum

ICD = implantable cardioverter-defibrillator

LVEF = left ventricular ejection fraction

***m*IBG** = *meta*-iodobenzylguanidine

NYHA = New York Heart Association

PET = positron emission tomography

SCD = sudden cardiac death

SPECT = single-photon emission computed tomography

Myocardial Scar

The extent of myocardial scar is predictive of inducibility of ventricular arrhythmias at electrophysiologic study (5), and it has been reported to be more predictive of total mortality (6,7) and SCD than is LVEF. Morishima et al. (8) reported that single-photon emission computed tomography (SPECT) myocardial perfusion defect size at rest was the strongest predictor of lethal arrhythmic events over 30 months of follow-up among 106 patients with MADIT II (Multicenter Automatic Defibrillator Implantation Trial II) criteria for ICD placement. Cardiac magnetic resonance (CMR) with late gadolinium enhancement has been used to demonstrate myocardial scar in patients with nonischemic and ischemic cardiomyopathy. In some patients with nonischemic cardiomyopathy, SCD is believed to result from the presence of myocardial scar (9,10), which provides a substrate for reentrant ventricular arrhythmias (Figs. 1 and 2). Wu et al. (11) performed a prospective study of 65 patients with nonischemic cardiomyopathy prior to ICD placement with a median follow-up of 17 months for end points of SCD or appropriate ICD discharge. End points were detected in 22% of patients with CMR evidence of myocardial scar versus only 8% of patients without evidence of gadolinium enhancement ($p = 0.03$).

Myocardial Ischemia

Ischemia, including myocardial ischemia at rest (hibernation), is recognized as a trigger for ventricular arrhythmias (12,13). Revascularization that alleviates ischemia reduces the rate of inducibility of ventricular arrhythmias at electrophysiologic study (14) and reduces the incidence of SCD (15). van der Burg et al. (16) reported that survivors of SCD who were found to have jeopardized myocardium on dipyridamole perfusion imaging, and who then underwent revascularization, had a relatively low rate of death or recurrent ventricular arrhythmia (14% over 3 years). In comparison, patients not revascularized had a 38% rate of death or recurrent ventricular arrhythmia over 3 years ($p < 0.05$). Elhendy et al. (17) followed 90 patients with coronary disease who received an ICD for primary or secondary prevention of SCD. In this study, 72% of patients had undergone prior coronary artery bypass surgery. Ischemia manifest as new or worsening wall motion abnormality on stress echocardiography was an independent predictor of death and ICD therapy during 2.8 ± 1.5 years of follow-up (Fig. 3). In the Coronary Artery Bypass Graft Patch study, 900 patients with LVEF <36% and abnormal signal-averaged electrocardiogram were randomized to receive or not receive an ICD at the time of coronary artery bypass graft surgery. There was no difference in the incidence of sustained ventricular tachycardia or ventricular fibrillation between the groups. The authors speculated that complete surgical revascularization with relief of ischemic substrate may have explained the lack of benefit of ICD implantation in these apparently high-risk patients (18).

Combined Myocardial Ischemia and Scar

There is evidence that the total extent of myocardial scar plus ischemia may provide stronger prediction of major ventricular arrhythmias (19) and SCD compared with either measurement alone. Piccini et al. (20) analyzed a cohort of 6,383 patients with angiographically documented coronary artery disease who underwent SPECT myocardial perfusion imaging. Sudden cardiac death occurred in 215 patients (3.4%) over 6.1 years of follow-up. After adjustments for LVEF and clinical variables, the summed stress score, representing fixed plus reversible defects on SPECT myocardial perfusion im-

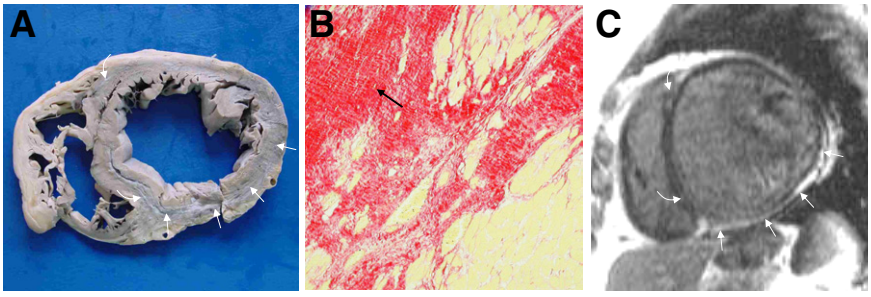

Figure 1. Pathologic and Cardiac Magnetic Resonance Demonstration of Myocardial Fibrosis in Nonischemic Cardiomyopathy

(A) Pathologic short-axis section through the left and right ventricles at mid-ventricular level showing mid-wall fibrosis **(straight arrows)** in the inferior, lateral, and septal walls from a patient with nonischemic dilated cardiomyopathy. **(B)** Sirius red staining confirming the presence of collagen in a microscopic section from the area of fibrosis in the pathologic section. **(C)** Premortem cardiac magnetic resonance image of the same myocardial slice illustrating the correlation of areas of late gadolinium enhancement with pathologic fibrosis. Reproduced with permission from Assomull et al. (10).

ages, remained significantly associated with the occurrence of SCD. Among perfusion indices, only the summed stress score was predictive of SCD on adjusted analysis, suggesting that the combination of scar and ischemia has greater predictive power than either scar or ischemia alone (Fig. 4). Further support for this concept arose from a CMR study by Yan et al. (21) of 144 patients with coronary artery disease and myocardial delayed enhancement following gadolinium-diethylenetriamine penta-acetic acid administration. Core myocardial infarct zones were identified by having gadolinium signal intensity more than 3 standard deviations above that of remote normal myocardium. Peri-infarction zones were identified as having signal-intensity thresholds 2 to 3 standard deviations greater than remote normal regions. After adjustments for age and LVEF, the percentage of the total infarct area localized to the peri-infarct zone was independently associated with cardiovascular mortality with a hazard ratio of 1.49 ($p = 0.01$). These CMR methods have also been applied to the prediction of sustained monomorphic ventricular tachycardia during electrophysiologic study or device interrogation (19). For 20 patients inducible with monomorphic ventricular tachycardia and 27 patients who were not inducible, there

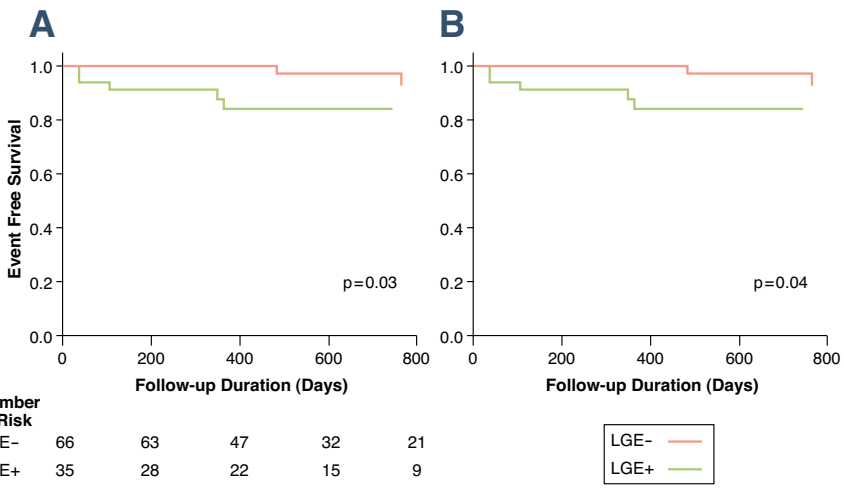

Figure 2. Prediction of Sudden Cardiac Death by LGE

(A) Kaplan-Meier estimates for the combined end point of sudden cardiac death and sustained ventricular tachycardia with the presence (LGE+) or absence (LGE−) of LGE. **(B)** The same data adjusted for baseline differences in left ventricular ejection fraction. Reproduced with permission from Assomull et al. (10). LGE = late gadolinium enhancement.

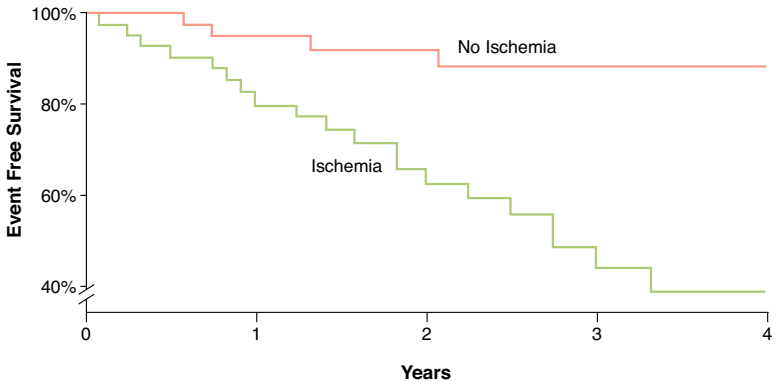

Figure 3. Prediction of Sudden Cardiac Death or Implantable Cardioverter-Defibrillator Therapy by Myocardial Ischemia

Kaplan-Meier curves indicating freedom from sudden cardiac death and appropriate implantable cardiac defibrillator therapy in patients with coronary artery disease at high risk for arrhythmic death. Risk is stratified by the presence or absence of myocardial ischemia detected by stress echocardiography. Independent predictors of events in the Cox multivariate model were a history of spontaneous sustained ventricular tachycardia (hazard ratio [HR]: 1.9; 95% confidence interval [CI]: 1.3. to 3.8; $p < 0.01$), inducible ventricular tachycardia on electrophysiologic study (HR: 1.7; 95% CI: 1.2 to 4.5; $p < 0.01$), and myocardial ischemia (HR: 2.1; 95% CI: 1.2 to 3.5; $p < 0.01$). Reproduced with permission from Elhendy et al. (17).

were no baseline differences in CMR measurements of LVEF, LV volumes, and infarct size. By multivariate analysis, the extent of the peri-infarction hyperenhancement zone was the only significant predictor of inducibility for monomorphic ventricular tachycardia. These studies suggest an important role of peri-infarction myocardial ischemia in addition to the extent of myocardial infarction scar for the prediction of risk for ventricular tachycardia and SCD. Myocardial perfusion imaging and echocardiography are widely available and relatively inexpensive for quantitative assessment of the extent of myocardial ischemia and scar. Cardiac magnetic resonance imaging and cardiac computed tomography also hold substantial potential for assessment of the extent of myocardial ischemia and scar, but further study is needed to establish the relative value of these newer and more costly resources.

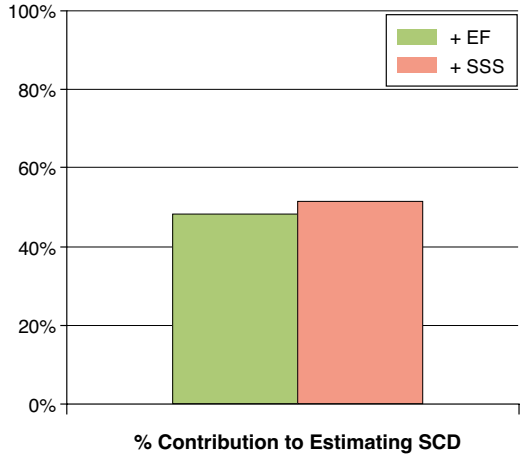

Figure 4. Prediction of SCD From Combined Myocardial Ischemia and Scar

Relative contribution of the extent of myocardial ischemia plus scar to estimating sudden cardiac death (SCD) when compared with clinical risk factors and left ventricular ejection fraction (LVEF). When compared with the clinical index, LVEF contributes 48.3% of the prognostic model content for estimating SCD. By comparison, the combination of EF + summed stress score (SSS) contributes 51.6% of the prognostic model content for estimating SCD, with the addition of SSS providing only a modest improvement in information content (20).

Sympathetic Innervation

Although coronary, myocardial, and valvular heart disease usually provide the structural substrate, sympathetic nervous system activation is often the trigger for life-threatening ventricular arrhythmias. Impaired global LV sympathetic innervation and regional myocardial sympathetic heterogeneity are arrhythmogenic (22) and can be imaged with planar (Fig. 5) (23) and/or SPECT imaging with *meta*-iodobenzylguanidine (*m*IBG) labeled with radioactive iodine (^{123}I) (24) or by positron emission tomography (PET) with tracers including hydroxyephedrine labeled with radioactive carbon (^{11}C) (25). The importance of adrenergic stimulation in the outcome of patients with heart failure is supported by prediction based on plasma norepinephrine levels (26) and measures of spillover of norepinephrine from the heart into the systemic

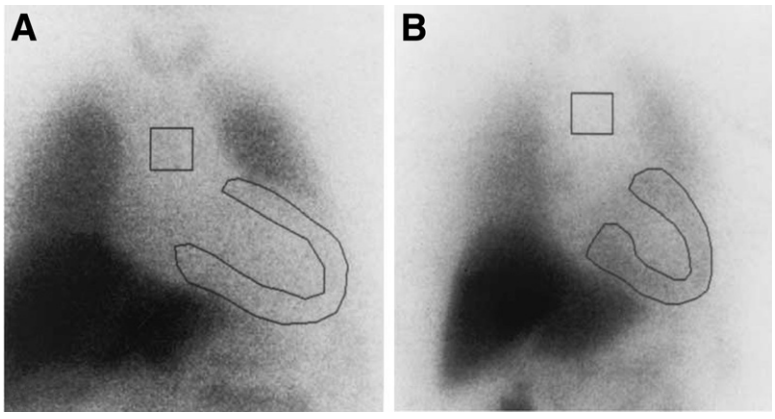

Figure 5. H/M Ratio of Sympathetic Nerve Activity From [^{123}I]*meta*-iodobenzylguanidine

Example of the heart to mediastinum (H/M) ratio calculated from a [^{123}I]*meta*-iodobenzylguanidine planar anterior image. **(A)** Image from a patient with severe heart failure (H/M ratio 1.02). **(B)** Image from a patient with moderate heart failure (H/M ratio 1.55). Reproduced with permission from Gerson et al. (23).

circulation (27). Beta-2 adrenergic receptor stimulation can initiate ventricular tachycardia by non–re-entrant mechanisms in the setting of heart failure (28). Indirect evidence for the importance of the sympathetic nervous system in arrhythmogenesis comes from the effectiveness of beta-adrenergic blocking drugs in the prevention of life-threatening cardiac arrhythmias and SCD (29).

Sympathetic nervous system imaging with [^{123}I]*m*IBG has been shown to be an effective predictor of mortality, and specifically of SCD, in patients with heart failure. In a study of 112 patients with nonischemic dilated cardiomyopathy, NYHA functional class II to IV heart failure and LVEF <40%, Merlet et al. (30) found the heart to mediastinum (H/M) ratio of [^{123}I]*m*IBG and the LVEF to be the only independent predictors of mortality over 27 ± 20 months of follow-up. Mortality was not predicted by the maximum consumption of oxygen during exercise, invasive measures of right heart pressure, plasma norepinephrine, or LV diastolic dimension. Importantly, the H/M ratio of [^{123}I]*m*IBG at 4 h after tracer injection was the only independent predictor of SCD. Numerous small studies have confirmed the capability of [^{123}I]*m*IBG imaging to identify patients at increased risk for spontaneous ventricular tachycardia (31–34), ventricular fibrillation (34,35), appropriate discharge of an ICD (36,37), and SCD (38,39). Preliminary results have been reported from paired phase III clinical trials including 964 patients with heart failure and 110 control subjects imaged with [^{123}I]*m*IBG and followed for 2 years for end points of cardiac death, heart failure progression, sustained ventricular arrhythmia, aborted cardiac arrest, or ICD discharge (40). Patients with an H/M ratio <1.20 had a 10-fold increase in major cardiac events compared with patients with an H/M ratio ≥1.60. When the analysis was restricted to patients with LVEF <30%, an H/M ratio <1.6 remained a significant predictor of major cardiac events compared with patients with an H/M ratio ≥1.60. Approximately 40% of study patients had an ICD during follow-up facilitating detection of arrhythmic events. An H/M ratio <1.6 was a significant predictor of major arrhythmic events.

Clinical Implications

The ICD is an effective but costly tool for prevention of SCD. Currently, therapies that cost <$50,000 per year of life saved are considered to be an appropriate use of medical financial resources. Selection of patients for ICD placement based on LVEF alone appears to select some subgroups in which the ICD is cost effective and other subgroups in whom it is not (e.g., patients who die from progressive heart failure or in whom no life-threatening arrhythmia occurs). Cardiac sympathetic imaging has demonstrated an independent ability to predict life-threatening arrhythmias, beyond prediction by LVEF alone. Impaired global and regional sympathetic nerve function images can reasonably be expected to improve the positive predictive value for identification of patients at highest risk for SCD. Cardiac imaging of myocardial scar, ischemia, and innervation all show substantial promise for improvement in accuracy of prediction of arrhythmic death compared with the use of LVEF alone.

Future Directions

Future patient selection for ICD placement may rely on the use of combinations of imaging modalities that may complement or replace primary reliance on LVEF. One of the more promising approaches is the assessment of imbalance of myocardial perfusion and innervation. The presence of an innervation/perfusion mismatch, in which a peri-infarction zone of sympathetic denervation extends beyond the area of myocardial scar, provides a potential substrate for reentrant or triggered ventricular arrhythmias and arrhythmic death (9,22,41,42). Hayashi et al. (43) followed 40 patients with prior myocardial infarction, sustained ventricular arrhythmia, and ICD placement for 2 years with serial noninvasive electrophysiologic studies. In their study, the extent of innervation/perfusion mismatch was related to long-term variability in induced arrhythmias and was predictive of the emergence of spontaneous ventricular tachycardia or fibrillation. In addition to the presence and extent of myocardial scar, demonstration by perfusion imaging of the presence of viable myocardium, with reduced blood flow and chronic regional dysfunction (i.e., hibernating myocardium), has been shown to identify an important substrate for ventricular tachycardia and fibrillation (12). In a chronic porcine model of left anterior descending coronary artery occlusion, Sasano et al. (25) found regionally impaired catecholamine uptake and storage using PET imaging in the normally perfused border zone around the infarct (Fig. 6). The border zone containing an innervation/perfusion mismatch was the site of earliest activation of ventricular tachycardia on electrophysiologic testing (Fig. 7). Reduced survival in a context of hibernating myocardium and reduced LV function (44) is likely related, at least in part, to arrhythmic death (45). An ongoing multicenter study (PAREPET [Prediction of Arrhythmic Events with Positron Emission Tomography]) uses PET imaging of myocardial perfusion with ammonia labeled with radioactive nitrogen (^{13}N) and sympathetic innervation with ^{11}C-hydroxyephedrine to assess risk for SCD in patients with ischemic cardiomyopathy and LVEF <35%. The study is designed to assess the contributions of hibernating myocardium and myocardial denervation to the genesis of SCD in patients with ischemic cardiomyopathy (46).

Imaging assessment of regional inhomogeneity of adrenergic innervation also holds promise for identifying patients with heart failure at risk for SCD. In patients with ventricular tachycardia, in the absence of underlying coronary artery disease, regional sympathetic denervation detected by [^{123}I]*m*IBG imaging has been reported, whereas it was absent in patients without ventricular tachycardia (47). In a study of 11 patients with sustained ventricular

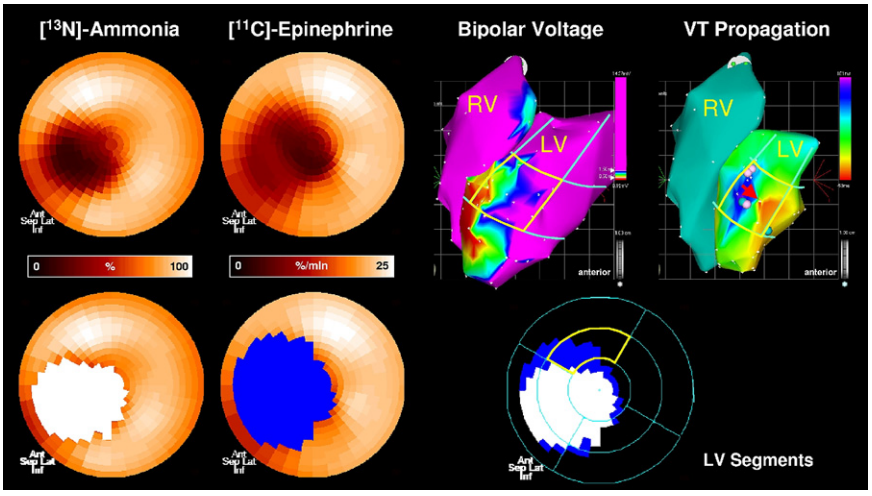

Figure 6. Perfusion/Innervation Mismatch and VT Site of Origin

Correlation of perfusion/innervation mismatch location and site of earliest activation of ventricular tachycardia (VT) in an animal model of VT. **(Left, top)** Positron emission tomography polarmaps show regional distribution of perfusion with ^{13}N-ammonia and of sympathetic innervation by ^{11}C-epinephrine retention. **(Left, bottom)** Extent maps of reduced perfusion and innervation. **(Right, bottom)** The extent of denervation exceeds the region of hypoperfusion, producing a mismatch. **(Right, top)** Three-dimensional electroanatomic maps, depicted in an anterior projection, show reduced bipolar endocardial voltage in the apex and distal anteroseptal wall. Propagation maps show the earliest activation of VT in the infarct border zone in the distal anterior wall **(red arrow)**. Reproduced with permission from Sasano et al. (25). LV = left ventricular; RV = right ventricle.

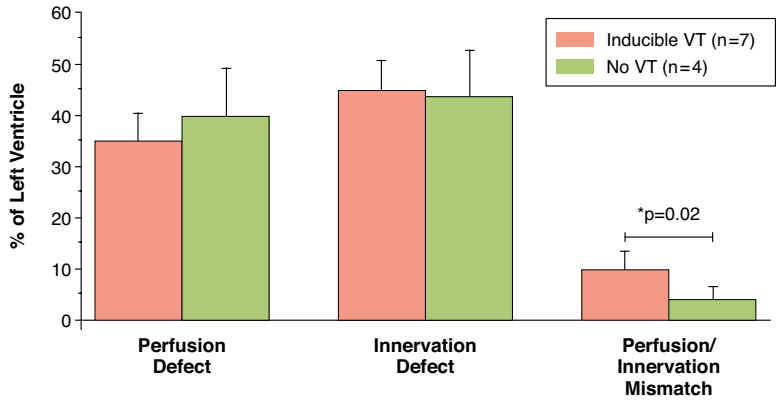

Figure 7. Perfusion/Innervation Mismatch and Inducibility of VT

In experimental animals with a mid-left anterior descending artery occlusion, positron emission tomography perfusion and innervation defect size was not significantly different in animals inducible for ventricular tachycardia (VT) compared with animals that were not inducible. Animals that were inducible for VT had more extensive perfusion/innervation mismatch size compared with animals that were not inducible for VT ($p = 0.019$). Reproduced with permission from Sasano et al. (25).

tachycardia or SCD, Calkins et al. (48) performed ^{11}C-hydroxyephedrine imaging followed by electrophysiologic mapping at the time of defibrillator implantation. The effective refractory period in myocardial regions with reduced ^{11}C-hydroxyephedrine retention was prolonged significantly compared with regions with normal tracer retention. These findings provide a correlation of scintigraphic evidence of regional sympathetic neuronal dysfunction and abnormal ventricular refractoriness in the human heart, thereby predisposing to re-entrant arrhythmias. Clinicians imaging regional sympathetic innervations must take into account the baseline heterogeneity of sympathetic nerve distribution in normal individuals and must also overcome the technical challenges of accurately quantitating regional sympathetic activity in a context of reduced global sympathetic innervation resulting from heart failure. In this regard, the superior spatial resolution of PET imaging may prove advantageous relative to [^{123}I]*m*IBG SPECT imaging.

Improved prediction of life-threatening ventricular arrhythmias may be facilitated by combining predictive data from imaging studies with nonimaging tests associated with electrical instability or with assays of neurohumoral substances. For example, reduced heart rate variability, a marker of impaired cardiac sympathetic nerve function, is associated with an increased risk of SCD following myocardial infarction. Although results from small initial studies were variable (36,49,50), recently Tamaki et al. (51) evaluated 106 patients with chronic heart failure (LVEF <40%) with baseline [^{123}I]*m*IBG imaging, signal-averaged electrocardiogram, time and frequency domain heart rate variability parameters, and measurement of QT interval dispersion. After 65 ± 31 months of follow-up, 18 of 106 patients had died suddenly. By multivariate Cox analysis, LVEF by radionuclide blood pool scan and [^{123}I]*m*IBG washout rate >27% were independently associated with SCD (Fig. 8), whereas data from signal-averaged electrocardiogram, heart rate variability, and QT dispersion were not predictive. Of note, abnormal washout of [^{123}I]*m*IBG was independently predictive of SCD, not only in patients with LVEF ≤35% but also in patients with LVEF >35% (Fig. 9). Others have observed that patients with low heart rate variability 3 months following myocardial infarction have an increased extent of innervation/perfusion mismatch (52), but prognostic studies combining heart rate variability and innervation/perfusion mismatch are not yet available. Other noninvasive electrophysiologic approaches for identification of patients likely to benefit from ICD placement have produced variable results, including microvolt T-wave alternans assessment. None of these approaches has been adequately assessed in conjunction with imaging assessment of myocardial scar, ischemia, and innervation.

Cardiac sympathetic nerve imaging has also been compared with or combined with data from plasma neurohormone levels in an attempt to improve prediction of major arrhythmic events. In a study of 337 patients with heart failure and LVEF ≤35%, B-type natriuretic peptide (BNP) has been shown to be an independent predictor of SCD (53). Nagahara et al. (37) used a combination of [^{123}I]*m*IBG and plasma BNP concentration in 54 patients to predict lethal cardiac arrhythmias resulting in appropriate ICD discharge or SCD. By multivariate analysis, only the [^{123}I]*m*IBG 4-h H/M ratio was independently

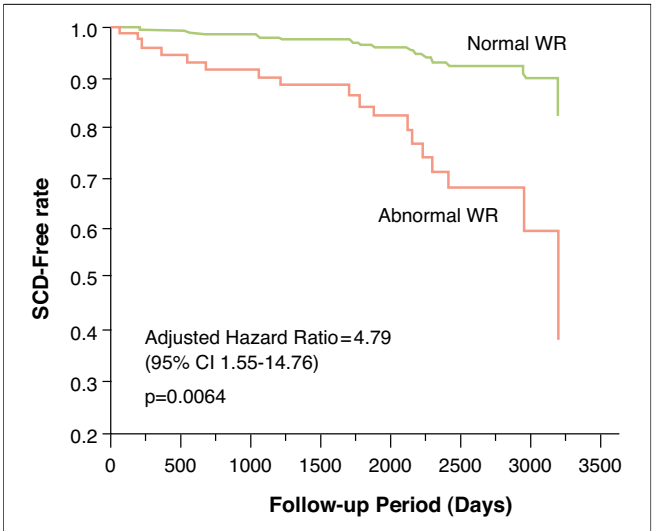

Figure 8. [^{123}I]*meta*-iodobenzylguanidine Prediction of SCD

Sudden cardiac death (SCD)-free survival rate following adjustment for age, gender, and left ventricular ejection fraction based on [^{123}I]*meta*-iodobenzylguanidine normal washout rate (WR) ≤27% versus abnormal washout rate >27%. Reproduced with permission from Tamaki et al. (51).

predictive of lethal arrhythmic events. In this study, the optimal cut-off level for BNP of 187 pg/ml did not identify any additional patients who developed lethal ventricular arrhythmia, compared with the optimal cut-off level for a high-risk H/M ratio ≤1.95. Additional promising areas of investigation for patient selection for ICD placement include imaging of myocardial metabolism and imaging to compare myocardial innervation with adrenergic receptor density (54).

Conclusions

Optimal selection of patients with heart failure for ICD placement will require additional predictive information beyond NYHA functional class, time following myocardial infarction, and LVEF. Identification and quantification of myocardial scar and ischemia can aid in detecting a high-risk anatomic and physiologic substrate for electrical instability. Imaging evaluation of cardiac sympathetic innervation shows clear prognostic potential. Combinations of imaging and indices of electrical instability appear promising for refining prediction of life-threatening ventricular arrhythmias (55). It remains to be seen if a combination of imaging and electrophysiologic variables can provide sufficient accuracy to enable identification of the majority of patients who will develop SCD despite having LVEF >35%. Imaging and electrophysiologic measures are also needed to identify patients in NYHA class II or III heart failure who are likely to die from heart failure, not arrhythmic death, and therefore will not benefit from ICD placement. The time has come for large, multicenter clinical trials to document the optimal combination of LVEF, cardiac sympathetic innervation imaging, myocardial ischemia and

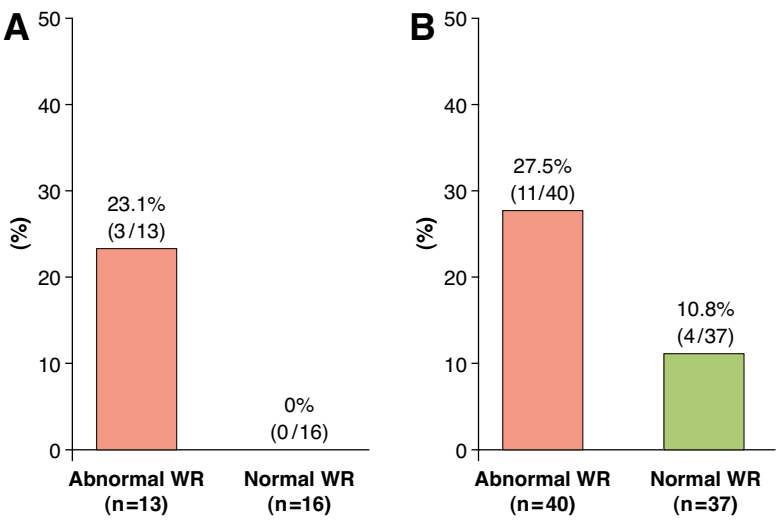

Figure 9. [^{123}I]*meta*-iodobenzylguanidine Prediction of Sudden Cardiac Death in Patients With Left Ventricular Ejection Fraction >35%

Sudden cardiac death rates by [^{123}I]*meta*-iodobenzylguanidine washout rate (WR) >27% (abnormal) versus ≤27% (normal). **(A)** Patients with left ventricular ejection fraction >35%. **(B)** Patients with left ventricular ejection fraction ≤35%. Reproduced with permission from Tamaki et al. (51).

scar imaging, neurohormonal assay (BNP), and electrophysiologic assessment to substantially improve the identification of patients with heart failure for ICD placement. The recent preliminary report of results of a large, multicenter clinical trial (40) strongly suggests that an opportunity to save lives and medical expense will be squandered if the role of sympathetic nerve imaging is not clearly defined and is not the modality entered into the decision-making process for ICD placement in patients with heart failure.

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Key Words: implanted cardioverter defibrillator ■ sympathetic nervous system ■ [^{123}I]*meta*-iodobenzylguanidine ■ [^{11}C]hydroxyephedrine ■ cardiac magnetic resonance ■ heart failure.