Published in final edited form as:

J Nucl Cardiol. 2016 December ; 23(6): 1322–1334. doi:10.1007/s12350-015-0392-0.

Life Threatening Ventricular Arrhythmias: Current Role of Imaging in Diagnosis and Risk Assessment

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Abstract

Sudden cardiac arrest continues to be a major cause of death from cardiovascular disease but our ability to predict patients at the highest risk of developing lethal ventricular arrhythmias remains limited. Left ventricular ejection fraction is inversely related to the risk of sudden death but has a low sensitivity and specificity for the population at risk. Nevertheless, it continues to be the main variable considered in identifying patients most likely to benefit from implantable defibrillators to prevent sudden death. Imaging myocardial sympathetic innervation with PET and SPECT as well as imaging characteristics of myocardial infarcts using gadolinium enhanced cardiac magnetic resonance are emerging as imaging modalities that may further refine patient selection beyond ejection fraction. This review will primarily focus on employing advanced imaging approaches to identify patients with left ventricular dysfunction that are most likely to develop lethal arrhythmias and benefit from inserting a primary prevention implantable cardiac defibrillator. While not yet tested in prospective studies, we will review risk prediction models incorporating quantitative imaging and biomarkers that have been developed that appear promising to identify those at highest risk of sudden death.

Keywords

Sudden Cardiac Arrest; Risk Stratification; ^{11}C -hydroxyephedrine; ^{125}I -metaiodobenzylguanidine; Gadolinium MRI

Despite major advances in the diagnosis and treatment of coronary artery disease and congestive heart failure, sudden cardiac arrest (SCA) remains a major public health problem in the United States(1). This is underscored by the fact that as the mortality from cardiovascular disease has declined over the last 40 years, the number of sudden deaths per year has remained fairly constant. What has appeared to change over this time is the arrhythmic cause of SCA with a declining frequency of ventricular fibrillation and an increasing incidence of pulseless electrical activity and asystole(2). The latter may be a

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Disclosures

No disclosures

primary cause of SCA but could also reflect the cessation of electrical activity over time after cardiac arrest that originates as ventricular fibrillation. While some episodes of SCA occur during the acute phase of a myocardial infarction, the majority are primarily arrhythmic events that occur without clinical evidence of an acute coronary syndrome.

Clinical investigation has thus far focused on identifying and treating the patients at highest risk of SCA from lethal ventricular arrhythmias. Patients at highest risk include those having heart failure with depressed systolic left ventricular function and patients with inheritable genetic disorders placing them at high risk of SCA. Significant advances have been made in treating selected subgroups of patients. Nevertheless, there are several sobering observations regarding the current approaches that are available to identify and treat those at risk of SCA. First, as recently summarized(3), nearly half of all sudden deaths occur in patients without a prior diagnosis of heart disease making the rapid initiation of cardiopulmonary resuscitation the only currently available approach to treat these patients (Table 1). Of the equally large number developing SCA with established heart failure or stable ischemic heart disease, a minority (~14%) have depressed left ventricular systolic function. Thus, few would be candidates to receive a primary prevention implantable cardiac defibrillator (ICD) based on current evidence based guidelines. Finally, there has been considerable basic and clinical investigation into genetic abnormalities (e.g. ion channel abnormalities and hypertrophic cardiomyopathy) but these comprise a small number of the events (~2%). Thus, despite the magnitude of the problem and considerable clinical investigation, we currently have no additional approaches to identify the majority of patients who develop sudden cardiac arrest. Although left ventricular ejection fraction (LVEF) has no direct relationship to the electrical activity of the heart and only identifies a small fraction of the patients at risk, it remains the standard of care for selecting high risk patients most likely to benefit from primary prevention ICDs.

Because of these limitations, there continues to be considerable interest in developing novel imaging approaches to assess functional and anatomic substrate factors potentially associated with arrhythmic risk. These have largely focused on either quantifying myocardial sympathetic innervation or characterizing more detailed myocardial anatomic substrates such as fibrosis and myocardial scar volume. This review will primarily focus on studies using imaging to select patients at highest risk for primary prevention of SCA that already have a depressed LVEF. While encouraging results have been obtained, all of the imaging approaches remain investigational and none has been approved for selecting patients at risk of cause specific mortality from SCA. Readers interested in the use of imaging to assess arrhythmic risk in inherited disorders associated with SCA are referred to recent reviews(4).

Research Challenges Facing Investigators Evaluating Imaging Approaches to Predict SCA

The methodologies developed to use advanced cardiac imaging modalities to identify substrate factors associated with SCA are fairly straightforward. Nevertheless, the end-points used to define clinically relevant arrhythmic events vary widely among published studies

making it difficult to pool observations on their prognostic value. Furthermore, the majority of studies are small and retrospective in nature. Several small studies have evaluated cause specific mortality from sudden death using contemporary adjudication methods but most have evaluated composite primary end-points. While composite end-points are helpful in using an imaging approach to assess prognosis, they frequently include outcomes related to heart failure that may be of limited value in identifying patients most likely to benefit from device therapies to prevent arrhythmic events leading to SCA. An obvious example is that a single chamber primary prevention ICD will prevent SCA from ventricular fibrillation (VF) but it won't have an impact on death due to pump dysfunction. Thus, the ideal imaging approach should be able to predict the likelihood of developing SCA independently from the competing risk of death from heart failure.

The second major problem facing clinical trials of imaging in predicting the risk of SCA relates to the increasing need to employ prospective observational studies that rely on surrogate end-points like appropriate ICD therapies. The clearest surrogate end-point for SCA would be ICD discharge for ventricular fibrillation. Defibrillation for fast ventricular tachycardia (VT>240 bpm, which is at times difficult to distinguish from VF on recorded ICD electrogram), is also felt to be a closer surrogate end-point for SCA. This is supported by the observation that the frequency of therapy for VF or fast VT approximate the benefit of primary prevention ICD device therapy on survival(5). Nevertheless, the majority of trials evaluating novel imaging approaches have included all appropriate ICD therapies as surrogates for lethal ventricular arrhythmias which greatly overestimate the actual frequency of sudden death in the population at risk (at least 3-fold). It is now clear that the majority of ventricular arrhythmias treated with conventional ICD programming are short-lived and self-terminating without progressing to VF or sustained VT. For example, in the Multicenter Automatic Defibrillator Implantation Trial–Reduce Inappropriate Therapy, increasing the time to detect and treat ventricular arrhythmias not only reduced occurrence of appropriate ICD therapies (76%) but less aggressive programming surprisingly also improved survival (6).

Finally, most available studies evaluating imaging modalities that may help predict the risk of SCA are retrospective, have referral bias and, as stated above, employ composite primary end-points that commonly reflect a variety of adverse outcomes other than arrhythmic death. Most include patients with ischemic as well as nonischemic cardiomyopathy and many also include both patients receiving ICDs for secondary prevention of SCA and patients receiving ICDs for primary prevention. Very few studies have attempted to develop multiple parameter risk models combining biomarkers, high risk clinical variables and imaging. Of the prediction models developed, none have yet been validated in prospective clinical trials. These limitations are not unique to imaging studies and are also present in many studies that employ alternate approaches for risk stratification for SCA such as those assessing aspects of cardiac electrical activity and cardiac biomarkers(2). The remainder of this review will summarize the current status of imaging autonomic dysfunction and myocardial scar to predict the risk of developing life threatening arrhythmias in primary prevention ICD candidates with acquired forms of heart disease.

Myocardial sympathetic denervation and the risk of SCA

Alterations in cardiac sympathetic activity have been linked to disease progression and increased mortality in cardiovascular disease (7). Advances in cardiac molecular imaging have resulted in the development of radiolabeled norepinephrine analogs that can quantify myocardial sympathetic innervation in-vivo. These are normally taken up into the presynaptic sympathetic nerve terminal by the norepinephrine transporter (Figure 1). Two have been studied the most extensively. ^{123}I -meta-iodobenzylguanidine (^{123}I -*m*IBG) is a SPECT tracer which has been approved by the FDA for imaging cardiac sympathetic innervation to determine prognosis in patients with heart failure. The investigational positron emitting agent ^{11}C -meta-hydroxyephedrine (^{11}C -HED) is the principal PET tracer which has been used in research studies quantifying regional sympathetic denervation. Despite an ever growing body of evidence demonstrating an association between radiotracer based assessment of cardiac sympathetic denervation with ventricular arrhythmias and SCA, none are currently approved to select patients for cardiac device therapy.

Global cardiac sympathetic denervation and event-free survival

Initial studies evaluating the prognostic significance of cardiac sympathetic denervation examined the relationship between outcomes and the global heart to mediastinum ratio (HMR) of ^{123}I -*m*IBG in small clinical populations of mixed ischemic and non-ischemic cardiomyopathy. In a cohort of 90 patients with cardiomyopathy, Merlet et al. found that the HMR was the strongest predictor of survival over short-term follow up (8). These findings were subsequently expanded to show that the ^{123}I -*m*IBG HMR was the most significant clinical predictor of cardiac mortality (9). The predictive capacity of global ^{123}I -*m*IBG was independent of the etiology of left ventricular dysfunction, and also provided prognostic value among those with only mildly reduced LVEF (40–50%) (9).

These initial studies paved the way for the multicenter ADMIRE-HF study (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure), which is the largest prospective study evaluating global ^{123}I -*m*IBG uptake and clinical outcomes. In this study, planar ^{123}I -*m*IBG and SPECT perfusion imaging were performed in 961 patients with New York Heart Association class II or III heart failure and LVEF<35 (10). The majority of patients (66%) had ischemic cardiomyopathy. Over a median follow-up of 17 months, the primary composite end-point (including heart failure progression, all arrhythmic events and cardiac death) occurred more frequently among those with a global reduction in myocardial ^{123}I -*m*IBG uptake (prospectively defined as a late HMR<1.6). Although the frequency of arrhythmic events was significantly higher among those with a HMR < 1.6, the vast majority of events were non-sustained VT. Sudden death, resuscitated SCA and appropriate ICD discharges (including shock as well as anti-tachycardia pacing) were a small portion of the total composite endpoints (21%) (10). Quantification of regional defects in a subgroup of patients did not provide any additional value in predicting prognosis (10).

A sub-analysis of the ADMIRE-HF study explored whether ^{123}I -*m*IBG HMR improved risk stratification over LVEF. ADMIRE-HF LVEF values reported by the core laboratory (some > 35%) were stratified by a late HMR of 1.6 and composite end-points were estimated in each group (11). A late HMR of <1.6 conferred a greater risk of death and arrhythmic events

across all LVEF subgroups. Interestingly, among subjects with relatively preserved function (LVEF > 40%), a HMR>1.6 was associated with an excellent prognosis with no mortality or arrhythmic events in the follow-up period. In contrast, individuals having an LVEF>40% and a late HMR<1.6 had a 7.5% per 100 person-years risk of death and composite arrhythmic events. This retrospective post-hoc analysis raises the possibility that imaging sympathetic innervation in patients with only mildly depressed LV function could aid in identifying the large number of patients at risk of SCA who are currently not considered candidates based on LVEF (3, 12).

Verschure et al. performed a patient level meta-analysis to determine the prognostic endpoint that was most highly associated with altered global ^{123}I -mIBG uptake(13). Over a mean follow-up of 37 months, the HMR was able to predict all categories of cardiac events. The strongest predictive values were for composite cardiac events, all-cause mortality, and total cardiac mortality. Interestingly, the weakest univariate predictor of global ^{123}I -mIBG HMR was for arrhythmic events. In multivariate analysis, only heart failure class and age were independently associated with arrhythmias.

Global cardiac sympathetic denervation and cause specific mortality from sudden death and/or surrogate arrhythmic end-points

Tamaki et al. showed that cardiac ^{123}I -mIBG imaging could also predict the subsequent development of cause specific mortality from SCA in 106 patients with a LVEF < 40%(14). Three indices of sympathetic denervation were derived from ^{123}I -mIBG imaging - early HMR (at 20 min), delayed HMR (at 200 min) and the ^{123}I -mIBG washout ratio (between 20 minutes and 200 minutes after injection). Over an average follow up of 5.4 years there were 18 events and each of the ^{123}I -mIBG indices were predictors of SCA(14, 15). In multivariate analysis, only the washout ratio and LVEF remained independent predictors of SCA. Patients with a rapid washout ratio (>27%) had a significantly greater risk of SCA (hazards ratio: 4.8, 95% confidence interval: 1.6–14.8). This predictive value was also seen among subjects with a LVEF >35%(14). Other ^{123}I -mIBG indices as well as signal –averaged electrocardiogram, heart rate variability and QT dispersion were not independent predictors of SCA. It should be noted that there were several exclusion criteria for this study, most notably the use of beta-blockers at the time of imaging. Since optimal medical therapy can favorably improve the washout ratio (16–18), the generalizability of this early study to the contemporary management of patients that are usually imaged on medical therapy for heart failure remains unclear. Despite this caveat, this study is particularly significant since it is the only one available that did not include surrogate end-points such as ICD therapies and only included cause specific mortality from SCA as its primary end-point.

A post-hoc analysis of the ADMIRE-HF study showed a relationship between HMR on planar imaging and arrhythmic events (defined as a composite of SCA, appropriate ICD therapy, resuscitated cardiac arrest or sustained ventricular tachycardia). In this analysis, Al Badarin et al. evaluated 778 patients from the original ADMIRE-HF cohort who did not have an ICD at the time of ^{123}I -mIBG imaging(19). These patients had a composite arrhythmic event rate of 6.9% and 9.4% at 1 and 2 years respectively. A HMR<1.6 (hazards ratio: 3.5, 95% confidence interval: 1.5–8), an LVEF<25% (hazards ratio: 1.9, 95%

confidence interval: 1.2–3.0) and a systolic blood pressure <120 mm Hg (hazards ratio: 1.2, 95% confidence interval: 1.0–1.4) were independent predictors of arrhythmic events. The ADMIRE-HF risk score developed using these variables demonstrated that a small subset of the population without them (~20%) was at low risk for arrhythmic events (discussed subsequently).

Regional cardiac sympathetic denervation, SCA and arrhythmic events

Global myocardial norepinephrine uptake is reduced from increased washout arising from increased myocardial sympathetic tone in viable myocardium as well as areas of regional sympathetic denervation. Some studies have evaluated whether inhomogeneity in sympathetic innervation increases the risk of SCA or surrogate arrhythmic end-points (Figure 1). Inhomogeneity in myocardial sympathetic innervation can occur in areas subjected to reversible ischemia as well as in fibrotic myocardial scars(20). Due to this, the ^{123}I -*m*IBG defect size in patients with coronary disease frequently exceeds infarct volume. This is best demonstrated in patients undergoing reperfusion with primary percutaneous coronary intervention for ST-segment elevation myocardial infarction (21, 22). Prominent regional denervation also develops following chronic repetitive ischemia without infarction and has been found in animal models of hibernating myocardium with both ^{123}I -*m*IBG (23) and ^{11}C -HED(24). In preclinical studies, viable dysfunctional myocardial regions can exhibit partial sympathetic denervation (25), evidence of reinnervation as reflected by sympathetic nerve sprouting (25, 26) and alterations in beta adrenergic receptor density (27). The translational relevance of these findings is underscored by the fact that animal models of viable dysfunctional myocardium exhibit one of the highest rates of spontaneous SCA from VF during brief sympathetic activation in the absence of infarction(28, 29).

Since regional myocardial sympathetic denervation is more technically challenging to quantify, there are fewer studies that have evaluated its prognostic significance. Nevertheless, the available data suggests that inhomogeneity and/or the extent of sympathetic denervation in humans may be more directly related to arrhythmic end-points and sudden death. Bax et al. provided one of the first clinical studies exploring the relation between regional sympathetic denervation and inducible arrhythmic events in 50 patients having an LVEF 40% who were referred for electrophysiological study for unexplained syncope or non-sustained VT(30). The 30 patients with a positive electrophysiological study had a significantly greater late ^{123}I -*m*IBG SPECT summed defect score compared to those with a negative electrophysiological study. There were no differences between groups in global ^{123}I -*m*IBG uptake (early or late HMR). The only independent predictor of a positive electrophysiological study (sustained VT) was the late summed ^{123}I -*m*IBG defect score reflecting the extent of regional denervation. Along similar lines, a recent study found reduced regional ^{123}I -*m*IBG uptake in scar border zones to predict VT inducibility during an electrophysiological study (31).

The ability of regional sympathetic denervation assessed using ^{123}I -*m*IBG and SPECT Technetium-99m perfusion imaging to predict spontaneous arrhythmic events (appropriate ICD therapies) was evaluated in a heterogeneous population of 116 patients. This cohort

included patients with both ischemic and nonischemic cardiomyopathy as well as those receiving an ICD for primary as well as secondary prevention of SCA (32). After an average follow up period of 23 months, appropriate ICD therapy (shock or anti-tachycardia pacing) occurred in 21% of the patients. Late ^{123}I -*m*IBG SPECT defect size and ICD implantation for secondary prevention (not primary prevention) were the only independent predictors of ICD therapy and all cause cardiac mortality. Appropriate ICD therapies were more prevalent among those with large ^{123}I -*m*IBG defects (summed rest score > 26) when compared to smaller defects.

Recently, PET with ^{11}C -HED was employed to quantify the extent of regional sympathetic denervation and predict the risk of SCA in primary prevention ICD candidates with ischemic cardiomyopathy (33, 34). This trial was motivated by the fact that PET imaging has significant technical advantages allowing regional defect size to be quantified more readily than SPECT ^{123}I -*m*IBG. The Prediction of Arrhythmic Events with Positron Emission Tomography trial, was a prospective observational cohort study powered to evaluate whether the volume of denervated myocardium, infarct volume or viable hibernating myocardium could predict increased cause specific mortality from sudden cardiac arrest (SCA) as its primary end point. The study enrolled 204 patients, who underwent PET assessment of myocardial perfusion ($^{13}\text{NH}_3$ – ammonia retention), myocardial denervation (^{11}C -HED) and viability (^{18}F -2-deoxyglucose during a glucose insulin clamp). After an average follow-up period of 4.1 years, thirty three patients experienced SCA. This endpoint included adjudicated arrhythmic death (SCA) or ICD discharge for aborted arrhythmic death (ventricular fibrillation or VT >240 beats/min). Other device therapies including treatments for VT at rates < 240 (ATP or ICD discharge) were not considered SCA surrogates. Patients developing SCA had a significantly greater volume of denervated myocardium as well as greater viable denervated myocardium when compared to those without SCA (Figure 2). Kaplan Meier survival analysis demonstrated that both denervated and viable-denervated myocardium predicted time to SCA. Every 1% increase in the volume of the denervated myocardium was associated with a 5.7% increase in the risk of SCA. Patients in the highest tertile of denervation had an SCA rate of 6.7% per year. In a multivariate analysis, the magnitude of denervated myocardium was the only independent predictor of SCA from PET. Other multivariate predictors of SCA included, left ventricular size (end-diastolic volume index), serum creatinine and the inability to take an angiotensin converting enzyme inhibitor or angiotensin receptor blocker. The LVEF was not predictive of appropriate ICD therapy in this population nor was infarct volume assessed with ^{18}F -2-deoxyglucose during a glucose insulin clamp. The ^{11}C -HED retention in normally innervated myocardial regions was not different among those with and without SCA in part reflecting the high prevalence of optimal medical therapy in these patients. A post-hoc analysis found integrated ^{11}C -HED uptake throughout the entire left ventricle to be predictive of SCA (area under the curve: 0.76 vs. 0.78 for ^{11}C -HED defect size)(35).

In summary, there is a growing body of literature demonstrating that imaging myocardial sympathetic innervation using a variety of radiopharmaceuticals can provide prognostic information regarding the course of ischemic and nonischemic cardiomyopathy. Much of this reflects the fact that increases in myocardial sympathetic nerve activity are associated with reduced myocardial uptake of norepinephrine analogues reflecting the progression of

congestive heart failure. These global abnormalities correlate with surrogate endpoints related to hospitalization as well as mortality from pump dysfunction. More recent studies have begun to evaluate cause specific endpoints that are associated with arrhythmic death. While none of these methods has been validated in prospectively studied cohorts, the regional quantification of denervated myocardium in viable as well as infarcted regions appears to hold promise in differentiating patients at low and high risk of arrhythmic death.

Myocardial scar and the risk of SCA

Fatal ventricular arrhythmias from VT that degenerate into VF are felt to originate in myocardial scars and surrounding border regions. Electrophysiological studies have suggested a greater risk for SCA among those with ischemic cardiomyopathy who have multiple areas of transmural infarction when compared to those with less extensive scars(36). In nonischemic cardiomyopathy the presence of midwall fibrosis has been reported to predict those at risk SCA(37). Thus, imaging myocardial scar may compliment LVEF to provide incremental prognostic value in terms of SCA. Both cardiac magnetic resonance and cardiac radionuclide imaging have been extensively studied in this regard.

Identification of Scar on Cardiac Magnetic Resonance

Cardiac magnetic resonance is an excellent tool for myocardial tissue characterization and has the additional advantage of greater spatial and temporal resolution as compared to SPECT or PET. Cardiac magnetic resonance with late gadolinium enhancement can readily quantify regions of myocardial scarring (Figure 3). The presence and extent of scar on gadolinium enhanced cardiac magnetic resonance has been shown to be related to composite cardiovascular outcomes in both ischemic cardiomyopathy (38) and nonischemic cardiomyopathy (39–41). Electrophysiological studies have suggested that heterogeneity with islands of viable myocardium and fibrotic tissue are a particularly arrhythmogenic substrate which cardiac magnetic resonance can identify as areas of intermediate intensity on LGE images. These regions are commonly referred to as the ‘gray zone’. They have been shown to correlate with reduced QRS voltage when mapping patients with inducible ventricular arrhythmias(42). Thus, using cardiac magnetic resonance, the infarcted myocardial region can be divided into a central core infarct zone and a peri-infarct gray zone extending both circumferentially to the viable remote region as well as transmurally to the viable subepicardium. While both regions can be quantified using semi-automated methods(43) there is currently no consensus among studies regarding the specific criteria used to define the gray zone. Investigators have used the signal intensity or the full-width-half-maximal approaches for determining core infarct from peri-infarct gray zone on late gadolinium enhanced cardiac magnetic resonance. Core infarct and peri-infarct gray zones can be identified as areas of the myocardium with signal intensity ≥ 3 standard deviations and signal intensity between 2 to 3 standard deviations of the remote myocardial region respectively(43, 44). Others have employed a full-width-half-maximal approach where core infarcts are identified as areas $\geq 50\%$ of the maximal signal intensity of the infarct, and peri-infarct gray zones as areas with signal intensity greater than the maximum signal intensity of viable myocardium but $<50\%$ of maximal signal intensity of the infarct (39, 43).

The relation between scar on Cardiac Magnetic Resonance, Arrhythmias and SCA

The extent of late gadolinium enhancement on cardiac magnetic resonance has been shown to be associated with arrhythmic outcomes, in heterogeneous populations referred for electrophysiological study as well as ICD placement for primary and secondary prevention. An early study of 48 patients with ischemic cardiomyopathy referred for electrophysiological study reported a significantly greater infarct mass and surface area among those with inducible VT as opposed to noninducible patients (38). Infarct mass and surface area were independent predictors of inducible VT while LVEF was not. In support of this, a recent study found that patients receiving appropriate ICD therapies had an absolute infarct size of 39 grams while those with no ICD therapy had an infarct size of 18 grams (45).

Given the pathophysiological significance of infarct heterogeneity in ventricular arrhythmias, recent cardiac magnetic resonance studies have focused on quantifying the scar gray-zone. A small study of patients undergoing ICD implants found that those with inducible monomorphic VT during electrophysiological testing had significantly larger peri-infarct gray zones when compared to those without (19 vs. 13 grams, $p=0.015$) (46). LVEF, infarct size and indices of left ventricular remodeling were not different. In another study (47) where appropriate ICD therapies were delivered to ~20% of patients with ischemic cardiomyopathy (median follow up of 8.5 months), the gray zone was the only independent predictor of VT (hazards ratio=1.5, $p=0.04$). Like other studies, LVEF was not predictive of appropriate ICD therapy in this population. In a similar patient population, all measures of scar by cardiac magnetic resonance (total, core infarct and gray zone) were predictive of ventricular arrhythmias (48). In this cohort, quantifying the core infarct and gray zone did not improve the prediction of VT in comparison to total scar size. While these studies report an association between scar characteristics on cardiac magnetic resonance with arrhythmic events, all used either inducible VT or aggregate ICD therapies as surrogates for life threatening ventricular arrhythmias. None of them evaluated SCA as an endpoint directly.

More recent studies have evaluated scar on cardiac magnetic resonance in relation to SCA and surrogate arrhythmic end-points more closely linked to SCA. The Prospective Observational Study of Implantable Cardioverter Defibrillators trial prospectively evaluated 235 patients with ischemic or nonischemic cardiomyopathy that received primary prevention ICDs (41). All patients underwent cardiac magnetic resonance with blinded quantification of core infarct and gray zone. Nineteen percent of the study population developed arrhythmic outcomes (ICD therapy for sustained VT >180 beats per minute or VF) or cardiac death. The gray zone on cardiac magnetic resonance and elevated high sensitivity c - reactive protein were the only independent predictors of outcome on multivariate analysis.

Other studies have failed to show relation between the gray zone and arrhythmias. In primary prevention ICD patients with ischemic and nonischemic cardiomyopathy, Gao et. al. found that total scar was the only significant predictor (hazards ratio: 1.4, $p=0.001$) of patients experiencing a composite end-point which included appropriate ICD therapy, aborted SCA and sudden cardiac death (39). The total cardiac magnetic resonance scar also had a high negative predictive value (86%) for predicting event-free survival. Scar gray zone did not stratify patients developing the composite end-point. Similarly, another study

enrolling patients with ischemic and nonischemic cardiomyopathy (with an LVEF above and below 30%), reported that a scar size of >5% of the LV myocardium was the only independent predictor of SCA or ICD therapy. The gray zone was not predictive of arrhythmic outcomes after adjusting for scar size.

In summary, currently available studies highlight the potential usefulness of cardiac magnetic resonance based assessment of scar to assess cardiovascular risk for composite endpoints including arrhythmic events and appropriate ICD therapies. While promising, there are limitations related to employing the available data to predict the risk of lethal arrhythmic events. First, multiple approaches for scar quantification have been proposed(49) and no consensus exists on the optimal methodology for risk stratification. The lack of a consistent approach is compounded by the large variability reported in the assessment of core and peri-infarct (gray) regions(48, 49). Second, like imaging myocardial sympathetic innervation, the majority of studies use primary end-points that were composite and include ICD therapies for many ventricular arrhythmias that could be self-terminating and not degenerate into lethal arrhythmias such as ventricular fibrillation. Thus, while the available studies demonstrate an association between myocardial scar on cardiac magnetic resonance and cardiac mortality as well as composite arrhythmic events that include multiple appropriate ICD therapies, the evidence supporting cardiac magnetic resonance to predict cause-specific mortality from sudden death remains limited at the present time.

Scar on Radionuclide Imaging and Relationship with Arrhythmic Events

While most recent literature has focused on assessing the relation between scar and arrhythmic events using cardiac magnetic resonance, previous studies have evaluated the relationship of scar on nuclear myocardial perfusion imaging with arrhythmic events and SCA. Morishima et al. determined the relationship between SPECT variables and SCA in 106 patients with ischemic cardiomyopathy and LVEF<30%, (50). Over a follow-up of 30 months, 13% of the patients experienced SCA. While they had significantly lower LVEF and greater left ventricular volumes, SPECT infarct size was the strongest predictor of SCA (hazards ratio: 6.3, 95% confidence interval: 1.8–22.8). In a secondary prevention population study, consecutive survivors of SCA with ischemic cardiomyopathy were enrolled to examine the relationship among ischemia, viability, scar and recurrent arrhythmic events (51). Those with extensive scar by SPECT (defined as scar involving >1 vascular territory) had significantly higher recurrent event rates when compared to those with less extensive or no scar (54% vs. 16%, $p<0.05$). On multivariate analysis, an extensive scar and LVEF 30% were the only independent predictors of death and recurrent ventricular arrhythmias.

The presence of myocardial scar on SPECT has been shown to further risk stratify patients with low HMR (<1.6) on ^{123}I -*m*BG imaging in patients with nonischemic cardiomyopathy(52). Among 317 patients from the ADMIRE-HF cohort, those with a late HMR <1.6 but a summed rest score ≥ 8 had fewer episodes of sustained VT, resuscitated SCA and appropriate ICD therapies when compared to those with a summed rest score ≥ 8 (3.9% vs. 11.9%, $p=0.001$). Hou et al. recently reported the prevalence of appropriate ICD therapy, VT and VF over an average follow up of 15 months and SPECT parameters(53). Patients who experienced the composite end point (39%) had significantly lower LVEF

(24% vs. 35%, $p<0.005$) and larger myocardial scar area (35% vs. 12%, $p<0.005$). Neither LVEF nor scar area predicted the occurrence of arrhythmic events on multivariate analysis. These findings are similar to those from the PAREPET study. In this study, PET infarct size (assessed using ^{18}F -2-deoxyglucose during a glucose insulin clamp) was not an independent predictor of arrhythmic events which included adjudicated sudden death or aborted SCA (ICD discharge for VF or VT>240 bpm) (34).

In summary, the currently available data from studies using radionuclide imaging is consistent in showing that scar volume is related to all cause cardiovascular mortality in patients with a depressed ejection fraction. While scar volume is also predictive of receiving appropriate ICD therapies, many of these may be treating self-terminating events that may not lead to SCA. Thus, when evaluating arrhythmic death and a more restrictive set of ICD surrogate end-points felt to be more directly associated with SCA, the PAREPET trial did not demonstrate a relation between scar volume and event free survival.

Imaging-based Risk Models for Predicting Life Threatening Arrhythmias

Risk prediction models incorporating multiple imaging parameters along with clinically relevant variables have only been evaluated in a few studies but have shown promise in developing risk scores that may better improve our ability to predict subgroups of patients at highest risk for arrhythmic events and cause specific mortality from SCA. Several of these risk models are briefly summarized in Table 2. While it is understandable that such an approach may have a low sensitivity, the high specificity conferred by this approach could provide a negative predictive value that is sufficient to identify those with a depressed ejection fraction at low risk of arrhythmic events. Several promising approaches are discussed in greater detail below.

An initial sub analysis of the ADMIRE-HF cohort demonstrated the combined value of imaging scar and sympathetic denervation for predicting composite arrhythmic events (sustained VT, resuscitated cardiac arrest and appropriate ICD therapy)(52). Arrhythmic events developed in 63 of 929 patients were ICD therapies (73%). When analyzed by etiology of heart failure, the HMR and infarct size (summed rest score: SRS) stratified those with nonischemic but not ischemic cardiomyopathy. Individuals with a HMR ≤ 1.6 and an infarct size of $<12\%$ of the LV had no arrhythmic events (high negative predictive value). Patients with both a low HMR and high scar burden had the highest risk (12%) of arrhythmic events. A subsequent analysis of patients without an ICD at the time of ^{123}I -*mIBG* imaging confirmed that a late HMR <1.6 , an LVEF $<25\%$ along with systolic blood pressure were independent predictors of composite events(19). The authors used these parameters to develop an ADMIRE-HF risk score to stratify the population (Figure 4). In another study, Kawai et al. prospectively evaluated the value of a risk score determined from delayed HMR and WR, on ^{123}I -*mIBG* imaging, in predicting SCA(54). The authors divided late HMR and WR into 6 grades from 0 to 5, according to the degree of deviation from control values, and based on these scores, the patients were divided into 3 groups: low (1 to 4), intermediate (5 to 7), and high (8 to 10). In this study a total of 16 of 81 patients experienced SCA during an average follow up period of 7 years. Patients with a low ^{123}I -

*m*IBG risk score had no events (high negative predictive value) but these progressively increased with increasing score category (intermediate 19% and high 36%, $p = 0.001$).

The PAREPET study developed a risk model to predict SCA using optimized cut-points for the four independent predictors of arrhythmic death identified from multivariate analysis (55). These included the amount of denervated myocardium (on ^{11}C -HED PET), LV end-diastolic volume, serum creatinine and lack of angiotensin inhibition. A PAREPET risk score was developed based on the number of risk factors present (0, 1 or 2). The annual rate of SCA was <1% when no risk factors were present, 4%/year with 1 risk factor and 12%/year for those with 2 risk factors (Figure 5). Importantly, nearly half of this primary prevention ICD population with ischemic cardiomyopathy was identified as low risk for SCA using this approach.

Cardiac MR has also been employed to develop a cardiovascular risk model. The PROSE-ICD study developed a risk model to predict arrhythmic events using late gadolinium enhanced cardiac magnetic resonance(41). In this study, high sensitivity c-reactive protein and scar gray-zone volume on late gadolinium enhanced cardiac magnetic resonance were predictive of arrhythmic events. The gray-zone and high sensitivity c-reactive protein were divided into tertiles to stratify the population. Patients in the lowest tertile of both gray-zone and high sensitivity c-reactive protein had an annualized event rate of 0.7% compared to the intermediate (5.6%/year) and highest risk groups (16%/year).

Collectively, these studies highlight the fact that a combination of risk factors including clinical, biomarker and imaging parameters (some employing multiple modalities) may provide a greater precision to risk stratify patients for SCA as opposed to single imaging parameters. While these approaches show great promise as risk prediction tools, none have yet been validated in prospective studies.

Summary

The use of newer cardiac imaging modalities to predict the risk of SCA in high risk subpopulations of patients with established heart disease and depressed left ventricular function has advanced substantially. Virtually all of these approaches are based upon quantitative rather than subjective image analysis. Thus, if prospectively validated, high throughput automated imaging analysis will be required for clinicians to incorporate the results into predictive algorithms as continuous variables of risk in practice. Assessing scar volume appears to correlate with composite cardiovascular outcomes including total cardiac mortality. The ability of scar volume to identify patients at risk of arrhythmic death using surrogate end-points that more closely correlate with the development of arrhythmic death remains untested. Analysis of myocardial sympathetic innervation currently has similar issues regarding the prediction of composite end-points not directly related to arrhythmic death. Nevertheless, several studies evaluating ^{123}I -*m*IBG washout in relation to SCA(54) as well as imaging regional denervation with PET in ischemic cardiomyopathy(55) provide promising data that support the ability of imaging myocardial sympathetic innervation to assess the relative risk of cause specific mortality from SCA in patients with a depressed ejection fraction. The next step is to prospectively validate risk prediction models to predict

SCA and compare strategies based upon competing imaging modalities in a head to head fashion. This will hopefully lead to an improved approach to identify patients at risk of sudden cardiac death that can be employed to identify those at risk in the large group of patients that have relatively preserved systolic function.

Acknowledgments

Supported by the National Heart Lung and Blood Institute (HL-055324, HL-061610), the Department of Veterans Affairs, the Albert and Elizabeth Rekate Fund in Cardiovascular Medicine and the National Center for Advancing Translational Sciences (UL1TR001412)

Abbreviations

SCA	sudden cardiac arrest
ICD	implantable cardioverter defibrillator
LVEF	left ventricular ejection fraction
VF	ventricular fibrillation
VT	ventricular tachycardia
¹²³I-<i>m</i>IBG	¹²³ I-meta-iodobenzylguanidine
¹¹C-HED	¹¹ C-meta-hydroxyephedrine
HMR	heart to mediastinum ratio
ADMIRE-HF	AdreView Myocardial Imaging for Risk Evaluation in Heart Failure
PAREPET	Prediction of Arrhythmic Events with Positron Emission Tomography

References

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. *Circulation*. 2015; 131:e29–322. [PubMed: 25520374]
2. Goldberger JJ, Basu A, Boineau R, Buxton AE, Cain ME, Canty JM Jr, et al. Risk stratification for sudden cardiac death: A plan for the future. *Circulation*. 2014; 129:516–26. [PubMed: 24470473]
3. Wellens HJ, Schwartz PJ, Lindemans FW, Buxton AE, Goldberger JJ, Hohnloser SH, et al. Risk stratification for sudden cardiac death: current status and challenges for the future. *Eur Heart J*. 2014; 35:1642–51. [PubMed: 24801071]
4. Nagueh SF, Zoghbi WA. Role of Imaging in the Evaluation of Patients at Risk for Sudden Cardiac Death: Genotype-Phenotype Intersection. *JACC Cardiovasc Imaging*. 2015; 8:828–45. [PubMed: 26183555]
5. Daubert JP, Wilber DJ, Lin A, Zareba W, Andrews ML, Huang DT, et al. ICD therapy for fast ventricular tachycardia or ventricular fibrillation is a surrogate endpoint for mortality in MADIT II. *Circulation*. 2003; 108:IV–385.
6. Moss AJ, Schugar C, Beck CA, Brown MW, Cannom DS, Daubert JP, et al. Reduction in inappropriate therapy and mortality through ICD programming. *N Engl J Med*. 2012; 367:2275–83. [PubMed: 23131066]
7. Shen MJ, Zipes DP. Role of the autonomic nervous system in modulating cardiac arrhythmias. *Circ Res*. 2014; 114:1004–21. [PubMed: 24625726]

8. Merlet P, Valette H, Dubois-Rande JL, Moyse D, Duboc D, Dove P, et al. Prognostic value of cardiac metaiodobenzylguanidine imaging in patients with heart failure. *J Nucl Med*. 1992; 33:471–7. [PubMed: 1552326]
9. Wakabayashi T, Nakata T, Hashimoto A, Yuda S, Tsuchihashi K, Travin MI, et al. Assessment of underlying etiology and cardiac sympathetic innervation to identify patients at high risk of cardiac death. *J Nucl Med*. 2001; 42:1757–67. [PubMed: 11752070]
10. Jacobson AF, Senior R, Cerqueira MD, Wong ND, Thomas GS, Lopez VA, et al. Myocardial iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure. *J Am Coll Cardiol*. 2010; 55:2212–21. [PubMed: 20188504]
11. Shah AM, Bourgoun M, Narula J, Jacobson AF, Solomon SD. Influence of ejection fraction on the prognostic value of sympathetic innervation imaging with iodine-123 *MIBG* in heart failure. *JACC Cardiovasc Imaging*. 2012; 5:1139–46. [PubMed: 23153914]
12. Chugh SS. Early identification of risk factors for sudden cardiac death. *Nat Rev Cardiol*. 2010; 7:318–26. [PubMed: 20421887]
13. Verschure DO, Veltman CE, Manrique A, Somsen GA, Koutelou M, Katsikis A, et al. For what endpoint does myocardial 123I-*MIBG* scintigraphy have the greatest prognostic value in patients with chronic heart failure? Results of a pooled individual patient data meta-analysis. *Eur Heart J Cardiovasc Imaging*. 2014; 15:996–1003. [PubMed: 24686260]
14. Tamaki S, Yamada T, Okuyama Y, Morita T, Sanada S, Tsukamoto Y, et al. Cardiac iodine-123 metaiodobenzylguanidine imaging predicts sudden cardiac death independently of left ventricular ejection fraction in patients with chronic heart failure and left ventricular systolic dysfunction: results from a comparative study with signal-averaged electrocardiogram, heart rate variability, and QT dispersion. *J Am Coll Cardiol*. 2009; 53:426–35. [PubMed: 19179201]
15. Kioka H, Yamada T, Mine T, Morita T, Tsukamoto Y, Tamaki S, et al. Prediction of sudden death in patients with mild-to-moderate chronic heart failure by using cardiac iodine-123 metaiodobenzylguanidine imaging. *Heart*. 2007; 93:1213–8. [PubMed: 17344327]
16. Kasama S, Toyama T, Hatori T, Sumino H, Kumakura H, Takayama Y, et al. Evaluation of cardiac sympathetic nerve activity and left ventricular remodelling in patients with dilated cardiomyopathy on the treatment containing carvedilol. *Eur Heart J*. 2007; 28:989–95. [PubMed: 17409109]
17. Toyama T, Hoshizaki H, Yoshimura Y, Kasama S, Isobe N, Adachi H, et al. Combined therapy with carvedilol and amiodarone is more effective in improving cardiac symptoms, function, and sympathetic nerve activity in patients with dilated cardiomyopathy: comparison with carvedilol therapy alone. *J Nucl Cardiol*. 2008; 15:57–64. [PubMed: 18242480]
18. de Peuter OR, Verberne HJ, Kok WE, van den Bogaard B, Schaap MC, Nieuwland R, et al. Differential effects of nonselective versus selective beta-blockers on cardiac sympathetic activity and hemostasis in patients with heart failure. *J Nucl Med*. 2013; 54:1733–9. [PubMed: 23970363]
19. Al Badarin FJ, Wimmer AP, Kennedy KF, Jacobson AF, Bateman TM. The utility of ADMIRE-HF risk score in predicting serious arrhythmic events in heart failure patients: incremental prognostic benefit of cardiac 123I-*mIBG* scintigraphy. *J Nucl Cardiol*. 2014; 21:756–62. quiz 3–55, 63–5. [PubMed: 25015681]
20. Barber MJ, Mueller TM, Henry DP, Felten SY, Zipes DP. Transmural myocardial infarction in the dog produces sympathectomy in noninfarcted myocardium. *Circulation*. 1983; 67:787–96. [PubMed: 6825234]
21. Matsunari I, Schricke U, Bengel FM, Haase HU, Barthel P, Schmidt G, et al. Extent of cardiac sympathetic neuronal damage is determined by the area of ischemia in patients with acute coronary syndromes. *Circulation*. 2000; 101:2579–85. [PubMed: 10840008]
22. Bengel FM, Barthel P, Matsunari I, Schmidt G, Schwaiger M. Kinetics of 123I-*MIBG* after acute myocardial infarction and reperfusion therapy. *J Nucl Med*. 1999; 40:904–10. [PubMed: 10452304]
23. Luisi AJ Jr, Fallavollita JA, Suzuki G, Canty JM Jr. Spatial inhomogeneity of sympathetic nerve function in hibernating myocardium. *Circulation*. 2002; 106:779–81. [PubMed: 12176946]
24. Luisi AJ Jr, Suzuki G, deKemp R, Haka MS, Toorongian SA, Canty JM Jr, et al. Regional ¹¹C-hydroxyephedrine retention in hibernating myocardium: Chronic inhomogeneity of sympathetic innervation in the absence of infarction. *J Nucl Med*. 2005; 46:1368–74. [PubMed: 16085596]

25. Fernandez SF, Ovchinnikov V, Canty JM Jr, Fallavollita JA. Hibernating myocardium results in partial sympathetic denervation and nerve sprouting. *Am J Physiol Heart Circ Physiol.* 2013; 304:H318–27. [PubMed: 23125211]
26. Chen PS, Chen LS, Cao JM, Sharifi B, Karagueuzian HS, Fishbein MC. Sympathetic nerve sprouting, electrical remodeling and the mechanisms of sudden cardiac death. *Cardiovasc Res.* 2001; 50:409–16. [PubMed: 11334845]
27. Iyer V, Canty JM Jr. Regional desensitization of β -adrenergic receptor signaling in swine with chronic hibernating myocardium. *Circ Res.* 2005; 97:789–95. [PubMed: 16141409]
28. Pizzuto MF, Suzuki G, Banas MD, Heavey B, Fallavollita JA, Canty JM Jr. Dissociation of hemodynamic and electrocardiographic indexes of myocardial ischemia in pigs with hibernating myocardium and sudden cardiac death. *Am J Physiol Heart Circ Physiol.* 2013; 304:H1697–707. [PubMed: 23585137]
29. Canty JM Jr, Suzuki G, Banas MD, Verheyen F, Borgers M, Fallavollita JA. Hibernating myocardium: Chronically adapted to ischemia but vulnerable to sudden death. *Circ Res.* 2004; 94:1142–9. [PubMed: 15016734]
30. Bax JJ, Kraft O, Buxton AE, Fjeld JG, Parizek P, Agostini D, et al. 123 I-*mIBG* scintigraphy to predict inducibility of ventricular arrhythmias on cardiac electrophysiology testing: a prospective multicenter pilot study. *Circ Cardiovasc Imaging.* 2008; 1:131–40. [PubMed: 19808530]
31. Zhou Y, Zhou W, Folks RD, Manatunga DN, Jacobson AF, Bax JJ, et al. I-123 *mIBG* and Tc-99m myocardial SPECT imaging to predict inducibility of ventricular arrhythmia on electrophysiology testing: a retrospective analysis. *J Nucl Cardiol.* 2014; 21:913–20. [PubMed: 24858625]
32. Boogers MJ, Borleffs CJ, Henneman MM, van Bommel RJ, van Ramshorst J, Boersma E, et al. Cardiac sympathetic denervation assessed with 123-iodine metaiodobenzylguanidine imaging predicts ventricular arrhythmias in implantable cardioverter-defibrillator patients. *J Am Coll Cardiol.* 2010; 55:2769–77. [PubMed: 20538172]
33. Fallavollita JA, Luisi AJ Jr, Michalek SM, Valverde AM, deKemp RA, Haka MS, et al. Prediction of ARhythmic Events with Positron Emission Tomography: PAREPET study design and methods. *Contemp Clin Trials.* 2006; 27:374–88. [PubMed: 16647885]
34. Fallavollita JA, Heavey BM, Luisi AJ Jr, Michalek SM, Baldwa S, Mashtare TL Jr, et al. Regional myocardial sympathetic denervation predicts the risk of sudden cardiac arrest in ischemic cardiomyopathy. *J Am Coll Cardiol.* 2014; 63:141–9. [PubMed: 24076296]
35. Malhotra S, Fallavollita JA, Canty JM Jr. Comparable value of threshold and nonthreshold based techniques of cardiac sympathetic denervation assessment for predicting sudden cardiac arrest. *J Nucl Cardiol.* 2015; 22:775.
36. Stevenson WG, Brugada P, Waldecker B, Zehender M, Wellens HJ. Clinical, angiographic, and electrophysiologic findings in patients with aborted sudden death as compared with patients with sustained ventricular tachycardia after myocardial infarction. *Circulation.* 1985; 71:1146–52. [PubMed: 3995708]
37. Assomull RG, Prasad SK, Lyne J, Smith G, Burman ED, Khan M, et al. Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy. *J Am Coll Cardiol.* 2006; 48:1977–85. [PubMed: 17112987]
38. Bello D, Fieno DS, Kim RJ, Pereles FS, Passman R, Song G, et al. Infarct morphology identifies patients with substrate for sustained ventricular tachycardia. *J Am Coll Cardiol.* 2005; 45:1104–8. [PubMed: 15808771]
39. Gao P, Yee R, Gula L, Krahn AD, Skanes A, Leong-Sit P, et al. Prediction of arrhythmic events in ischemic and dilated cardiomyopathy patients referred for implantable cardiac defibrillator: evaluation of multiple scar quantification measures for late gadolinium enhancement magnetic resonance imaging. *Circ Cardiovasc Imaging.* 2012; 5:448–56. [PubMed: 22572740]
40. Nazarian S, Bluemke DA, Lardo AC, Zviman MM, Watkins SP, Dickfeld TL, et al. Magnetic resonance assessment of the substrate for inducible ventricular tachycardia in nonischemic cardiomyopathy. *Circulation.* 2005; 112:2821–5. [PubMed: 16267255]
41. Wu KC, Gerstenblith G, Guallar E, Marine JE, Dalal D, Cheng A, et al. Combined cardiac magnetic resonance imaging and C-reactive protein levels identify a cohort at low risk for defibrillator firings and death. *Circ Cardiovasc Imaging.* 2012; 5:178–86. [PubMed: 22267750]

42. Stevenson WG, Friedman PL, Sager PT, Saxon LA, Kocovic D, Harada T, et al. Exploring postinfarction reentrant ventricular tachycardia with entrainment mapping. *J Am Coll Cardiol.* 1997; 29:1180–9. [PubMed: 9137211]
43. Flett AS, Hasleton J, Cook C, Hausenloy D, Quarta G, Ariti C, et al. Evaluation of techniques for the quantification of myocardial scar of differing etiology using cardiac magnetic resonance. *JACC Cardiovasc Imaging.* 2011; 4:150–6. [PubMed: 21329899]
44. Yan AT, Shayne AJ, Brown KA, Gupta SN, Chan CW, Luu TM, et al. Characterization of the peri-infarct zone by contrast-enhanced cardiac magnetic resonance imaging is a powerful predictor of post-myocardial infarction mortality. *Circulation.* 2006; 114:32–9. [PubMed: 16801462]
45. Zeidan-Shwiri T, Yang Y, Lashevsky I, Kadmon E, Kagal D, Dick A, et al. Magnetic resonance estimates of the extent and heterogeneity of scar tissue in ICD patients with ischemic cardiomyopathy predict ventricular arrhythmia. *Heart Rhythm.* 2015; 12:802–8. [PubMed: 25583153]
46. Schmidt A, Azevedo CF, Cheng A, Gupta SN, Bluemke DA, Foo TK, et al. Infarct tissue heterogeneity by magnetic resonance imaging identifies enhanced cardiac arrhythmia susceptibility in patients with left ventricular dysfunction. *Circulation.* 2007; 115:2006–14. [PubMed: 17389270]
47. Roes SD, Borleffs CJ, van der Geest RJ, Westenberg JJ, Marsan NA, Kaandorp TA, et al. Infarct tissue heterogeneity assessed with contrast-enhanced MRI predicts spontaneous ventricular arrhythmia in patients with ischemic cardiomyopathy and implantable cardioverter-defibrillator. *Circ Cardiovasc Imaging.* 2009; 2:183–90. [PubMed: 19808591]
48. de Haan S, Meijers TA, Knaapen P, Beek AM, van Rossum AC, Allaart CP. Scar size and characteristics assessed by CMR predict ventricular arrhythmias in ischaemic cardiomyopathy: comparison of previously validated models. *Heart.* 2011; 97:1951–6. [PubMed: 21917670]
49. Mesubi O, Ego-Osuala K, Jeudy J, Purtilo J, Synowski S, Abutaleb A, et al. Differences in quantitative assessment of myocardial scar and gray zone by LGE-CMR imaging using established gray zone protocols. *Int J Cardiovasc Imaging.* 2015; 31:359–68. [PubMed: 25352244]
50. Morishima I, Sone T, Tsuboi H, Mukawa H, Uesugi M, Morikawa S, et al. Risk stratification of patients with prior myocardial infarction and advanced left ventricular dysfunction by gated myocardial perfusion SPECT imaging. *J Nucl Cardiol.* 2008; 15:631–7. [PubMed: 18761265]
51. van der Burg AE, Bax JJ, Boersma E, Pauwels EK, van der Wall EE, Schalij MJ. Impact of viability, ischemia, scar tissue, and revascularization on outcome after aborted sudden death. *Circulation.* 2003; 108:1954–9. [PubMed: 14530201]
52. Sood N, Al Badarin F, Parker M, Pullatt R, Jacobson AF, Bateman TM, et al. Resting perfusion MPI-SPECT combined with cardiac 123I-*mIBG* sympathetic innervation imaging improves prediction of arrhythmic events in non-ischemic cardiomyopathy patients: sub-study from the ADMIRE-HF trial. *J Nucl Cardiol.* 2013; 20:813–20. [PubMed: 23864400]
53. Hou PN, Tsai SC, Lin WY, Cheng CM, Chiang KF, Chang YC, et al. Relationship of quantitative parameters of myocardial perfusion SPECT and ventricular arrhythmia in patients receiving cardiac resynchronization therapy. *Ann Nucl Med.* 2015
54. Kawai T, Yamada T, Tamaki S, Morita T, Furukawa Y, Iwasaki Y, et al. Usefulness of cardiac meta-iodobenzylguanidine imaging to identify patients with chronic heart failure and left ventricular ejection fraction <35% at low risk for sudden cardiac death. *Am J Cardiol.* 2015; 115:1549–54. [PubMed: 25851796]
55. Fallavollita JA, Heavey BM, Luisi AJ Jr, Michalek SM, Baldwa S, Mashtare TL Jr, et al. Regional myocardial sympathetic denervation predicts the risk of sudden cardiac arrest in ischemic cardiomyopathy. *J Am Coll Cardiol.* 2014; 63:141–9. [PubMed: 24076296]
56. Malhotra S, Fernandez SF, Fallavollita JA, Canty JM Jr. Prognostic Significance of Imaging Myocardial Sympathetic Innervation. *Current Cardiol Reports.* 2015; 17:62.

Figure 1. Schematic of Sympathetic Transmission

Schematic of sympathetic transmission and neuronal uptake of ¹¹C-HED (¹¹C-meta-Hydroxyephedrine) and ¹²³I-MIBG (¹²³I-Metaiodobenzylguanidine) for imaging of sympathetic neuronal innervation. Norepinephrine (NE) is synthesized and packaged in the presynaptic sympathetic nerve terminals and released into the synaptic cleft. Released NE binds to post synaptic receptors, is taken up via the presynaptic norepinephrine transporter (NET) for repackaging or is released into the circulation and exits the heart through the coronary venous circulation (not show). Both ¹¹C-HED and ¹²³I-MIBG are taken up into the presynaptic nerve terminals using the NET-dependent mechanism. VMAT= vesicular monoamine transporter, DOPA = 3,4-dihydroxyphenylalanine. Modified and reproduced with permission from Malhotra et al.(56).

Figure 2. Imaging of Myocardial Flow, Viability, and Sympathetic Innervation with Positron Emission Tomography

Reconstructed images summarizing retention of each isotope. Upper panel (A) shows a subject who experienced SCA. Infarct size (^{18}F -2-deoxyglucose, ^{18}F FDG) which was smaller than the volume of sympathetic denervation (reduced ^{11}C -HED). Within the region of viable but denervated myocardium (mismatch between reduced ^{11}C -HED and preserved ^{18}F FDG) there was reduced perfusion ($^{13}\text{NH}_3$ -ammonia) indicating hibernating myocardium. In contrast, the lower panel (B) shows a subject with fairly closely matched reductions in flow, infarct volume and sympathetic denervation. (ANT – anterior; INF – inferior; LAT – lateral; SEP – Septum). Reproduced with permission from Fallavollita et al.(55).

Figure 3. Late Gadolinium Enhanced Cardiac Magnetic Resonance from a Patient with Ischemic Cardiomyopathy and Sustained Ventricular Tachycardia

Late gadolinium enhanced cardiac magnetic resonance depicts patchy myocardial scar (between red chevrons and white arrows) in the lateral wall of the left ventricle.

Figure 4. Prediction of Arrhythmic Events by the ADMIRE-HF Score Risk Model

ADMIRE-HF risk score comprised of LVEF<25%, late HMR<1.6 and systolic blood pressure (SBP) of <120 mm Hg, 120 - 139 mm Hg and 140 mm Hg. Patients with a low risk score had a significantly lower event rate (2%) at 24 months of follow up when compared to those with intermediate (10%) and high risk scores (16%) ($p=0.001$). The annualized event rate among patients with a low ADMIRE-HF risk score was ~1%/year. Reproduced with permission from Al Badarin et al.(19)

Figure 5. Sudden Cardiac Arrest Risk Factor Model from PAREPET

PAREPET risk score based on retrospective analysis using the four independent risk parameters from multivariate analysis. These included the percent of the left ventricle that was denervated, left ventricular end-diastolic volume index, serum creatinine and the inability to take in angiotensin-converting enzyme inhibitor. Cut points were obtained from univariate models for each continuous parameter or the presence or absence of angiotensin inhibition therapy. Kaplan-Meier curves demonstrate highly significant differences in the incidence of SCA in relation to the number of risk factors present ($p < 0.0001$). Subjects with no risk factors (blue, 44% of cohort) had an annual rate of SCA $< 1\%$. Those with two or more risk factors (red, 20% of cohort) had an annual risk of SCA increased to $\sim 12\%$. Patients with one risk factor (green, 36% of cohort) had an intermediate risk of SCA ($\sim 4\%$ /year). With permission from Fallavollita et al. (55).

Table 1

Categories of Heart Diseases that Contribute to Sudden Cardiac Death.

Percentage of all SCA	
No diagnosis of heart disease	45%
Diagnosis of heart disease	
LVEF > 40%	40%
LVEF <40%	13%
Genetic arrhythmic risk	2%

SCA=sudden cardiac arrest; LVEF=left ventricular ejection fraction. Adapted from Wellens et al. (3).

Table 2

Selected Risk Models Employing Imaging to Predict the Risk of Sudden Cardiac Arrest.

Author (Ref #)	Patient population	Patients (n)	Outcome	Events (n)	Prediction Model	Results
¹²³I-mIBG						
Sood et al. (52)	ADMIRE-HF patients with ischemic and nonischemic cardiomyopathy, LVEF <35% and NYHA II-III HF.	929	Sustained VT, SCA and all appropriate ICD therapies.	63	Combination of late HMR and infarct size.	No arrhythmic events among those with HMR. 1.6 and infarct size <12% of the myocardium.
Al Badarin et al. (19)	ADMIRE-HF patients without ICD.	778	Sustained VT, SCA and all appropriate ICD therapies.	54	ADMIRE-HF risk score.	Increasing prevalence of arrhythmic events with increasing risk score.
Kawai et al. (54)	Ischemic and nonischemic cardiomyopathy and LVEF <35%.	81	SCA	16	0-5 point scale for both late HMR and WR. Risk score.	No arrhythmic events in patients with low late HMR+WR score.
¹¹C-HEd						
Fallavollita et al. (34)	PAREPET trial: ischemic cardiomyopathy and LVEF 35%.	204	SCA or ICD discharge for VT/VF >240 bpm;	33	Risk model combining denervated myocardium, LVEDV, serum Cr and lack of angiotensin inhibition.	Patients with no risk factors had a <1% annual risk of SCA.
Gadolinium-enhanced CMR						
Wu et al. (41)	PROSE-ICD trial: ischemic and nonischemic cardiomyopathy and LVEF < 35%.	235	Cardiac death and appropriate ICD discharge for VF and VT >180 bpm.	45	Tertiles of gray zone and hsCRP.	Patients in the lowest tertile of gray zone and hsCRP had a <1% annual risk of events.
SPECT						
Hou et al. (53)	Ischemic and nonischemic cardiomyopathy with CRT for 6 months.	51	Combination of ICD therapy, VT and VF; n=20.	20	Combination of median LVEF, scar area and PSD.	Better survival among those with LVEF>29%, scar area <23% and PSD <50°.

ADMIRE-HF=AdreView Myocardial Imaging for Risk Evaluation in Heart Failure; ¹²³I-mIBG=¹²³I-metaiodobenzylguanidine; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association; VT=ventricular tachycardia; VF=ventricular fibrillation; ICD=implantable cardioverter defibrillator; HMR=heart-to-mediastinal ratio; SBP=systolic blood pressure; SCA=sudden cardiac arrest; WR=washout ratio; ¹¹C-HEd=¹¹C-meta-hydroxyephedrine; PAREPET=Prediction of Arrhythmic Events with Positron Emission Tomography; PET=Positron Emission Tomography; LVEDV=left ventricular end-diastolic volume; Cr=creatinine; CMR=cardiac magnetic resonance; PROSE-ICD=Prospective Observational Study of Implantable Cardioverter Defibrillators; hsCRP=high sensitivity c-reactive protein; SPECT=Single Photon Emission Computed Tomography; CRT=cardiac resynchronization therapy and PSD=phase standard deviation.