Importance of individual patient characteristics when assessing the ability of cardiac adrenergic imaging to guide ICD use

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A major strength of radionuclide cardiac imaging is that its portrayal of underlying physiologic and molecular processes of cardiac disease can provide risk stratification better than other testing methods, thereby able to improve patient management. At the same time, one must consider that as with most testing modalities, clinical implications of nuclear cardiac image findings may differ depending on a patient's clinical circumstances. With regard to myocardial perfusion imaging that is the most commonly used technique, while its strong and independent prognostic utility for patients with coronary disease has been well accepted for many years, it was recognized early in its development that prognostic implications of image findings vary depending on individual patient clinical characteristics.¹

There are continuing efforts to develop nuclear cardiology techniques that assess and help manage conditions other than coronary disease, most notably heart failure (HF), a ubiquitous condition with high morbidity and mortality, expected to dramatically increase in prevalence over the next decades.² An important component of managing HF patients is judicious use of cardiac implantable electronic devices that, while promising improved survival and quality of life, often cause significant morbidity and are expensive.

Among such devices is the implantable cardioverter defibrillator (ICD) used to prevent arrhythmic cardiac death in HF patients otherwise expected to have meaningful survival. While in published guidelines left ventricular ejection fraction (LVEF) is customarily the key parameter for deciding whether a HF patient should receive an ICD,³ this approach has widely recognized flaws. Being a blunt measure of LV function that misses much important information, LVEF has been characterized as “simplistic,” with limited ability to predict arrhythmic death.⁴ In one report, more than 80% of patients who received an ICD did not use it over as long as 8 years.⁵

ADVANTAGES OF RADIONUCLIDE CARDIAC AUTONOMIC INNERVATION IMAGING

It is therefore advantageous to use parameters related to ventricular arrhythmic mechanisms for ICD patient selection. Among potential choices, cardiac adrenergic innervation imaging with ¹²³I-*m*IBG or analogous positron emission tomographic (PET) tracers such as carbon-11 hydroxyephedrine (¹¹C-HED), that more directly assess underlying arrhythmic origins, has consistently demonstrated independent ability to risk stratify arrhythmic risk, in most reports superior to LVEF and conventional parameters.^{6–8} In some reports, cardiac event free survival serves as a surrogate for the absence of a lethal arrhythmic outcome. In 1992 work by Merlet et al.,⁹ for 90 high-risk HF patients with a mean LVEF of 22% but who did not have an ICD (prior to routine use), cardiac ¹²³I-*m*IBG uptake predicted adverse cardiac outcomes independently of LVEF. The approximately 50 patients who had a heart-to-mediastinum ratio (HMR) > 1.2 all survived, meaning that at least for the short 7-month mean follow-up an ICD would not have been needed to prevent an adverse

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Adrenergic Imaging with ^{123}I -mIBG or Analogous PET Tracers

Planar HMR and Washout
Extent and Severity of Tomographic Adrenergic Defects
Adrenergic-Perfusion Mismatch

Cardiac Parameters

Etiology of Cardiac Dysfunction: Ischemic vs. Nonischemic
Previous Arrhythmic Event: Primary vs Secondary ICD Indication
Clinical Heart Failure Severity
Left Ventricular Size
Left Ventricular Ejection Fraction
Heart Rate Variability
B-type natriuretic peptide

Extracardiac Clinical Factors

Age	Sex
BMI	Blood Pressure
Diabetes Mellitus	Renal Function
Serum Sodium	Medication Use

Potential Complementary Imaging Modalities

MRI: Scar Burden and Presence of “Border Zones”
EAM: Location of Scar Sites with Low Bipolar Voltage Amplitude
Gated SPECT: Presence and Severity of Mechanical Dyssynchrony

Fig. 1. Cardiac parameters, extracardiac clinical factors and complementary imaging modalities that can enhance findings from adrenergic imaging to more effectively assess arrhythmic risk, and thereby better guide ICD use. BMI, body mass index; EAM, electroanatomic mapping; HMR, heart-to-mediastinum ratio; ICD, implantable cardioverter defibrillator; ^{123}I -mIBG, iodine-123 meta-iodobenzylguanidine; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography. “Border zones” are regions with mixtures of scar and viable tissue.

arrhythmic outcome. In the “AdreView Myocardial Imaging for Risk Evaluation in Heart Failure” (ADMIRE-HF) study of 961 patients having heart failure with reduced EF (HFrEF) referred for cardiac ^{123}I -mIBG imaging, for a 777 patient subset who did not initially have an ICD (study began before ICD guidelines were instituted), at 17-month median follow-up those with an HMR ≥ 1.6 ($\sim 20\%$ of study cohort), had an extremely low cardiac fatality rate of $< 2\%$, meaning that such patients were unlikely to have benefited from an ICD during the follow-up period.^{10,11}

In studies that looked specifically at arrhythmic events, typically defined for patients with an ICD as

spontaneous sustained (> 30 seconds) ventricular tachycardia (VT), a resuscitated cardiac arrest or an appropriate ICD discharge, or for those without an ICD a sudden cardiac death or arrest (SCD, SCA) in which there was reasonable suspicion of an arrhythmic cause, the ability of adrenergic imaging to identify lower risk has been consistent. In a 17 patient study of patients who had an ICD for a mean of 14 months, an ^{123}I -mIBG planar image derived HMR threshold of 1.54 significantly separated high versus low likelihood of having had an ICD discharge.¹² Importantly, though, incorporation into the analysis of a Holter monitor derived heart rate variability parameter identified a small subgroup of

patients who had received no ICD discharges, showing that combining other information with image findings can provide superior risk stratification. A subsequent larger prospective study of 54 HF patients with an ICD found that the HMR correlated significantly and independently with future appropriate ICD discharges and SCD independently of LVEF and B-type natriuretic peptide (BNP).¹³ In the ADMIRE-HF study, an arrhythmic event (not including SCD) occurred in 3.5% of subjects with an HMR ≥ 1.6 vs 10.4% for HMR < 1.6 . An analysis extending follow-up to 2 years (ADMIRE-HFX) found that no patient with an HMR ≥ 1.8 had an arrhythmic event.^{10,14}

Despite numerous studies showing strong arrhythmic risk stratification of ¹²³I-mIBG HMR, not all do so. Noteworthy is an analysis by Verschure et al. finding that while HMR correlated with HF events, transplantation referral and all-cause mortality, it had limited power in specifically assessing arrhythmic risk.¹⁵ Tomographic imaging that better portrays electrical heterogeneity, has been shown to predict ICD discharges. Boogers et al. reported that in 116 HFrEF patients (mean LVEF = 28%), an adrenergic summed dysinnervation defect score > 26 increased 3-year likelihood of ICD use from 5% to 52%.¹⁶ For 27 patients with HFrEF followed for 16 months, Marshall et al. saw that a tomographic defect score $\geq 31\%$ had a 67% positive predictive value and an 86% negative predictive value for an appropriate ICD discharge or SCD likely to be arrhythmic.¹⁷ At the same time, several studies have suggested that while higher tomographic defect scores increase arrhythmic risk, intermediately high scores, as well as intermediately abnormal HMR measurements, may have the highest risk,^{14,18,19} likely because an intermediate abnormalities better reflect electrical heterogeneity, and because patients with the most abnormal ¹²³I-mIBG studies are at higher risk for a pump failure death.

PET ¹¹C-HED adrenergic imaging, with better image resolution and more accurate identification of adrenergic deficit tissue, also has high arrhythmic risk stratification power. Most notably, in the Prediction of Arrhythmic Events with Positron Emission Tomography (PAREPET) trial, in which 204 patients with ischemic cardiomyopathies underwent ¹¹C-HED imaging, the summed adrenergic deficit score predicted, over 4 years, arrhythmic death or an ICD discharge for VT/VF. Image parameters predicted adverse arrhythmic events independently of BNP or LVEF.⁷ However, a key finding was that incorporation of additional parameters, i.e., the LV end-diastolic volume index (LVEDVI), serum creatinine, and the patient not taking angiotensin inhibition therapy, provided superior arrhythmic risk stratification as the 44% of cohort patients who had an

area of denervation $< 37.6\%$ and no abnormalities in these additional parameters (and were taking the medications) had a $< 1\%$ /year arrhythmic risk. Subsequent data analysis showed that while a larger LVEDVI, lack of angiotensin inhibition therapy, and elevated BNP enhanced the association of high-risk image findings with an arrhythmic event, a higher resting heart rate, older age, elevated creatinine, a larger left atrial volume index and a larger LVEDVI better predicted non-sudden cardiac death.²⁰ Thus, combining image data with cardiac and clinical parameters improves identification of patients likely to benefit from an ICD.

RELEVANCE OF DIFFERING HEART FAILURE ETIOLOGIES

It is important to recognize that PAREPET was limited to patients with ischemic cardiomyopathies (ICM), and may not similarly apply to patients with non-ischemic cardiomyopathies (NICM). Studies have shown similarities and differences between these regarding the correlation of adrenergic image findings with adverse events. Wakabayashi et al. reported that while the HMR threshold for predicting events in ischemic patients was 1.5, it was 2.02 for patients with HF of other etiologies, with also a higher death rate for ICM patients with lower HMR.²¹ In a sub-analysis of ADMIRE-HF data, Clements et al.²² observed that, compared with NICM subjects, those with ICM had more extensive and severe ¹²³I-mIBG SPECT abnormalities, and larger amounts of innervation-perfusion mismatch. While 2-year all-cause and cardiac mortality did not differ between the groups, with ICM cardiac mortality risk was highest for perfusion defects involving 20%-40% of myocardium, while with NICM cardiac mortality was highest for smaller perfusion abnormalities and more ¹²³I-mIBG-perfusion mismatch.

When considering the ability of adrenergic imaging to assess ICD utility, one must also consider that the likelihood of an arrhythmic death differs between ICM and NICM patients, affecting the predictive value of imaging. In the Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality (DANISH) study involving 565 patients, Køber et al. reported that an ICD does not improve 5-year survival in patients with NICM.²³ Although in part this may be from more pump failure deaths, another reason is that differing NICM etiologies do not pose the same arrhythmic risks. In contrast, ICM patients are continuously at risk of sudden plaque rupture provoking a lethal arrhythmia. Nakajima et al. observed that the mode of death in HF patients depends on both HF etiology and follow-up time.²⁴ For ICM patients, at 2-year follow-up 50% of deaths are sudden

and presumably arrhythmic, 38% are from pump failure, and 13% are associated with acute myocardial infarction (AMI), while at 5 years SCD decreases to 42%, while pump failure death increases to 40% and AMI to 18%. For NICM, the likelihood of SCD is always less, with a 24% frequency at 2-year follow-up and 26% at 5-year follow-up. Thus, while ^{123}I -mIBG may be effective in risk stratifying ischemic and non-ischemic HF patients in terms of overall mortality, given the differing likelihood and timing of arrhythmic events, this variable must be factored in when evaluating the prediction of ICD benefit.

As was found for PAREPET ICM patients, clinical characteristics also affect ICD utility in NICM patients. The Seattle Proportional Risk Model (SPRM) predicts increased likelihood of arrhythmic mortality in young males, those with less severe HF, low EF and higher body mass index, while in contrast there is increased the likelihood of non-arrhythmic mortality in patients with diabetes, renal dysfunction, abnormal blood pressure and hyponatremia. In a sub-analysis of the DANISH study, SPRM identified a subgroup for which ICD implantation resulted in a 37% relative reduction in all-cause mortality, up to a 55% reduction for patients when the more inclusive Seattle Heart Failure Model (SHFM) was factored in.²⁵ Such data further support the importance of considering clinical characteristics for more effective ICD use.

FACTORING IN THE INDICATION FOR ICD IMPLANTATION

A final issue that must be considered, one investigated in the study by Sazonova et al.²⁶ in this issue of the Journal of Nuclear Cardiology, is if adrenergic image arrhythmic risk stratification utility depends on whether ICD implantation is being considered to prevent SCD in someone who has not had sustained VT or SCA but is determined to be at increased risk, i.e., primary prevention, versus whether an ICD is being considered because of prior SCA, sustained VT, or syncope caused by a ventricular arrhythmia, i.e., secondary prevention.³ In their report, 80 subjects with prior (> 3 months) myocardial infarction, 49 with HFrEF referred for ICD implantation as primary prevention, and 31 with chronic HF regardless of LVEF referred for secondary prevention from being a SCA survivor or having experienced hemodynamically unstable VT or stable VT not the result of a reversible cause, underwent adrenergic imaging with ^{123}I -mIBG and perfusion imaging with thallium-199. Seventy-eight of the enrolled subjects (47 primary, 31 secondary) were followed 18 months for an ICD discharge, as well as cardiac death (although there were none of the latter). Other than LVEF being lower in

primary prevention subjects, there was no difference in patient characteristics. While there was no significant difference in imaging results, as might be expected by their having worse systolic function, primary prevention subjects trended toward lower early and late HMR, higher washout, and higher early and late summed ^{123}I -mIBG dysinnervation scores, and toward more perfusion abnormalities. As would be expected, there were more ICD discharges in the secondary than primary prevention group, 35.5% vs 14.9%, respectively ($P = 0.066$), in accord with findings in the aforementioned work by Boogers et al.¹⁶ A key result was that ^{123}I -mIBG arrhythmic risk stratification was better for secondary than for primary prevention subjects, reflected in highly significant receiver operating characteristic curves for tomographic ^{123}I -mIBG parameters in the former group. However, while statistical significance was not achieved for the primary prevention group, there was a consistent trend toward more abnormality for most of the ^{123}I -mIBG and perfusion parameters in subjects who had an ICD discharge, with the lack of statistical significance, as noted by the authors, likely a reflection of statistical underpowering and shorter follow-up than in most literature reports. Another important finding was that for the secondary prevention group, images parameters were more strongly predictive of ICD shock than LVEF, emphasizing the limitation of using LVEF for guiding ICD use, thereby supporting published data showing that adrenergic imaging helps identify patients with LVEFs > 35% who would benefit from an ICD.²⁷ Thus, despite limitations of study conclusions regarding differences between ^{123}I -mIBG imaging for primary versus secondary prevention ICD implantation, the authors' message of the need to consider this factor, and the importance of further investigating potential benefit of adrenergic imaging for assessing ICD benefit in patients with a normal or mildly reduced LVEF, is important.

FUTURE DIRECTIONS

It is clear that the crucial decision of whether to refer a patient for ICD implantation should not rely so heavily on LVEF as other parameters closer to underlying arrhythmic mechanisms are better, and therefore need to be researched more thoroughly to the satisfaction of expert investigators and clinicians managing the patients. There is solid evidence that adrenergic imaging with ^{123}I -mIBG or similar PET tracers can improve ICD patient selection, avoiding unneeded, potentially harmful device implantation, while also showing ability to identify otherwise unrecognized patients who will benefit. At the same time, there is robust evidence that other non-invasive imaging modalities effectively stratify arrhythmic risk, especially cardiac magnetic resonance

imaging (MRI) which, by assessment of both scar burden and presence of border zone regions with mixed scar and viable tissue, has strong arrhythmic stratification power.^{6,28} Even better, if logistically and financially feasible, would be combined hybrid imaging techniques superimposing adrenergic tracers images onto structural, i.e., MRI or CT, or onto electroanatomical images, the latter showing promise to improve identification of arrhythmogenic sites.²⁹ Increased mechanical dyssynchrony on ECG-gated SPECT is also associated with higher arrhythmic risk.³⁰ Nevertheless, for whatever imaging technique(s) are ultimately used, image findings must be interpreted in the context of individual patient characteristics, including underlying cardiac pathology and the patient's previous history of arrhythmias, as summarized in the Figure 1. Finally, one must always consider that disease is dynamic with continuously changing pathophysiology as disease progresses or responds favorably to treatment, so whatever evaluation methods are developed, appropriate testing intervals will need to be determined. Of course, no testing method will ever be 100% predictive, and thus risk–benefit must always be considered, with the goal of prolonging quality life.

Disclosures

The author has no conflicts of interest related to this work.

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