The role of nuclear cardiac imaging in risk stratification of sudden cardiac death

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Sudden cardiac death (SCD) represents a significant portion of all cardiac deaths. Current guidelines focus mainly on left ventricular ejection fraction (LVEF) as the main criterion for SCD risk stratification and management. However, LVEF alone lacks both sensitivity and specificity in stratifying patients. Recent research has provided interesting data which supports a greater role for advanced cardiac imaging in risk stratification and patient management. In this article, we will focus on nuclear cardiac imaging, including left ventricular function assessment, myocardial perfusion imaging, myocardial blood flow quantification, metabolic imaging, and neurohormonal imaging. We will discuss how these can be used to better understand SCD and better stratify patient with both ischemic and non-ischemic cardiomyopathy. (J Nucl Cardiol 2016;23:1380–98.)

Key Words: Sudden cardiac death • PET • SPECT • ischemic heart disease • MIBG • sympathetic innervation • hibernating myocardium

Abbreviations			
CFR	Coronary flow reserve	MPI	Myocardial perfusion imaging
CS	Cardiac sarcoidosis	SDS	Sum difference score
DCM	Dilated cardiomyopathy	SRS	Sum rest score
HCM	Hypertrophic cardiomyopathy	SSS	Sum stress score
H/M	Heart-to-mediastinum ratio		
MBF	Myocardial blood flow		

INTRODUCTION

Sudden cardiac death (SCD) currently accounts for up to 60% of all cardiac death in the adult population in the United States.[1,2] Despite recent advances in our understanding of cardiovascular disease and in cardiac care, effective primary prevention of SCD in the general population is still an aspiration.[3,4] The final common pathway in most cases is malignant ventricular arrhythmia.[5] Although the fundamental pathophysiology is complex, an underlying anatomical substrate can be identified in the majority of patients,[6] with the most frequent being attributed to ischemic heart disease, idiopathic dilated cardiomyopathy (DCM), and hypertrophic cardiomyopathy (HCM).[7]

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Current guidelines focus on the left ventricular ejection fraction (LVEF) as the primary measure for SCD risk stratification and patient management.[8,9] One-third of all SCD occur in patients with moderate to severe left ventricular (LV) systolic dysfunction (LVEF $\leq$ 35%).[10] In this group, primary prevention with an implantable cardioverter defibrillator (ICD) significantly prolongs survival.[11,12] However, numerous patients with higher LVEF are still at risk of SCD, but would not qualify for ICD placement according to current guidelines. Furthermore, only 35% of patients randomized for ICD placement in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) received appropriate shock therapy over a 3-year follow-up.[13] Taken together, these facts underscore the lack of sensitivity and specificity of LVEF alone in identifying patients who will suffer from SCD and the need for better markers for SCD.

Emerging data support the potential of cardiac imaging to understand the mechanisms of SCD beyond simple LVEF measurement.[14] In this review, we will focus on the possible benefits that nuclear cardiology imaging (including myocardial perfusion imaging (MPI), LV function assessment, accurate flow quantification, metabolic imaging and neurohormonal imaging) offers us to improve risk stratification of SCD in patients with ischemic and non-ischemic cardiomyopathy.

MECHANISMS OF SUDDEN CARDIAC DEATH

By definition ''sudden,'' the acute event is not often witnessed, and therefore SCD is difficult to study. In most cases, it is accepted that the final pathway is malignant ventricular arrhythmia.[15,16] The underlying mechanisms of ventricular arrhythmogenesis are complex but can simply be considered as the interaction between a structural or anatomic substrate (myocardial scar from prior myocardial infarction) and a functional trigger, such as ischemia.[5,6] In the adult population, most SCD occurs in the setting of an abnormal anatomic substrate from coronary artery disease (CAD),[7,17-19] and reentry is the most frequent mechanism of malignant ventricular arrhythmias. Scar and fibrosis create areas of heterogeneous electrophysiological response and aberrant conduction, particularly in the border zones of infarct. What's more, the presence of ischemia exacerbates regional heterogeneity, further predisposing to malignant arrhythmia,[20,21] as does the presence of altered sympathetic innervation.[22,23] This implies that these factors (scar, hibernation, ischemia, and innervation) may represent potential imaging targets in the evaluation of SCD in addition to LV function (Table 1).

LEFT VENTRICULAR FUNCTION

LVEF is currently the most studied and most commonly used cardiac imaging marker to assess risk for SCD and is used to guide appropriate therapy in both ischemic and non-ischemic cardiomyopathies. Many studies, dating back to the 1980s, quickly established that LVEF is a strong predictor for overall cardiac mortality.[24-26] Not surprisingly, this led to the use of LVEF as a criterion of enrollment in the large clinical trials for the evaluation of ICDs in primary prevention of SCD in the 1990s and 2000s. In the Multicenter Unsustained Tachycardia Trial (MUSTT), Buxton et al demonstrated that in a group of 704 patients with CAD and LVEF $\leq$ 40%, the risk of sudden cardiac arrest or fatal arrhythmia was significantly reduced in the group treated with ICD when compared with the group without (relative risk 0.24; 95% CI 0.13-0.45; $P < .001$).[27] The Multicenter Automatic Defibrillator Implantation Trial II (MADIT II), another large randomized trial comparing ICD to medical therapy in 1232 patients with LVEF $\leq$ 30%, had similar results. Over 20 months, the mortality rates were 19.8% in the medical group vs 14.2% in the ICD group, a 31% relative reduction in the risk of death.[11] Similar results were again observed in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). 2521 patients with NYHA class II or III heart failure (HF) and LVEF $\leq$ 35% were randomized to receive either an ICD, amiodarone or a placebo. Median follow-up was 45.4 months. Amiodarone had no effect on survival while ICD therapy decreased risk of death by 23% (0.77; 95% CI 0.62-0.96; $P = .007$).[12] It is thus well established that ICD use in patients with reduced LVEF leads to a decreased risk of death and explains why LVEF plays such an important role in current guidelines regarding the use of ICDs[8,9,28-31] (Table 2).

Nuclear cardiac imaging offers many ways to evaluate LV function and LVEF. This includes ECG-gated images as part of MPI using either single-photon emission computer tomography (SPECT) or positron emission tomography (PET) imaging, and also radionuclide angiography (RNA), also called multigated acquisition (MUGA) scan. The use of these modalities to assess LV function and predict cardiac death have all been validated in large studies. Hachamovitch et al, in a study with 5366 patients, demonstrated that LVEF measured with ECG-gated images as part of SPECT MPI was a strong predictor of cardiac death.[32] In this study, which aimed at determining the utility of combining perfusion and functional assessment in predicting

Table 1. Overview of the different modalities and their uses

Target	Imaging modality	Clinical relevance	Guidelines support
LVEF	RNA (MUGA) SPECT MPI PET MPI	LVEF is the most used predictor of SCD at present RNA is one of the most accurate and reliable modalities for LVEF measurement—it is used in assessment pre ICD therapy[36-39]	*Primary prevention:* LVEF is used to guide ICD therapy in primary prevention of SCD—see Table 2 Reevaluation of LVEF 6-12 weeks after myocardial infarction is recommended to assess the potential need for primary prevention ICD implantation—Class 1/C[9,29,31]
Areas of ischemia/scar	SPECT MPI (^{201}Tl or ^{99m}Tc Sestamibi/Tetrofosmin) PET MPI (^{82}Rb or $^{13}NH_3$)	Ischemia is a reversible cause of SCD[46] Perfusion scans can guide revascularization before ICD therapy Scar presence can help guide catheter ablation therapy[9] Scar is associated with increased risk of SCD[44,57,58,60]	*VT/VF:* Stress echocardiography or SPECT is recommended to detect silent ischemia in patients with VT/VF who have an intermediate probability of having CAD and abnormal ECG—Class 1/B[9] Urgent catheter ablation is recommended in patients with scar-related heart disease presenting with incessant VT or electrical storm—Class 1/B[9] Prompt and complete coronary revascularization is recommended to treat myocardial ischemia that may be present in patients with recurrent VT or VF—Class 1/C[9,31] *Primary prevention:* No specific recommendations regarding primary prevention of SCD Ischemia imaging is recommended to direct revascularization in stable ischemic heart disease (Class IIa/B) and in heart failure(Class IIa/C)[30,136-139] *Note:* in patients with stable ischemic heart disease; ischemia directed revascularization is being evaluated in the ISCHEMIA Trial (https://www.ischemiatrial.org/) and in patients with ischemic heart failure, ischemia imaging is being compared in the AIMI-HF (IMAGE HF I-A) trial[140]

Table 1. continued

Target	Imaging modality	Clinical relevance	Guidelines support
Myocardial blood flow	PET MPI (^{82}Rb, ^{15}O-H_2O or $^{13}NH_3$)	Impaired stress MBF and coronary flow reserve are associated with VT and possible SCD[54]	No specific recommendations with regard to patients with VT/VF nor primary prevention of SCD Position Statement from the American Society of Nuclear Cardiology and the Society of Nuclear Medicine and Molecular Imaging is under development
Viable myocardium	PET viability (perfusion/^{18}F-FDG) SPECT (^{201}Tl or ^{99m}Tc Sestamibi/Tetrofosmin)	Viable [hibernating] myocardium is an unstable electrical region, and it is associated with an increased risk of SCD[59] The extent of perfusion-metabolism mismatch [hibernation] can guide therapy[60,62-64]	No specific recommendations with respect to patients with VT/VF or primary prevention of SCD Viability imaging is recommended to direct revascularization in patients with heart failure and CAD (Class IIa/B-C)[30,137,138] *Note:* in patients with ischemic heart failure, viability imaging is being compared in the AIMI-HF (IMAGE HF I-A) trial[140]
Neurohormonal (cardiac sympathetic innervation)	SPECT (MIBG) PET (^{11}C-HED)	The volume of denervated myocardium as a continuous value is a strong independent predictor of SCD[92] Sympathetic innervation anomalies are associated with ventricular arrhythmias,[23,68] appropriate ICD therapy and increased risk of SCD[73,74,77,92]	No specific recommendations with regard to patients with VT/VF or primary prevention of SCD *Note:* MIBG SPECT is FDA approved for human use for scintigraphic assessment of myocardial sympathetic innervation in patient with heart failure and LVEF $\leq$ 35% [Iobenguane Iodine-123 package insert; GE Healthcare]

LVEF, Left ventricular ejection fraction; *RNA*, radionuclide angiography; *MUGA*, multigated acquisition scan; *SPECT*, single-photon emission computed tomography; *PET*, positron emission tomography; *MPI*, myocardial perfusion imaging; *SCD*, sudden cardiac death; *ICD*, implantable cardioverter defibrillator; *^{201}Tl*, Thallium-201; *^{99m}Tc*, Technetium-99m; *^{82}Rb*, Rubidium-82 chloride; *$^{13}NH_3$*, nitrogen-13 ammonia; *VT*, ventricular tachycardia; *VF*, ventricular fibrillation; *^{15}O-H_2O*, oxygen-15-water; *^{18}F-FDG*, fluorine-18-fluorodeoxyglucose; *MBF*, myocardial blood flow; *MIBG*, Iodine-123-metaiodobenzylguanidine; *^{11}C-HED*, carbon-11-*meta*-hydroxyephedrine; *FDA*, food and drug administration.

Table 2. Role of LVEF in current guidelines for ICD implantation in primary prevention[9,29-31]

Indication	LVEF cut-off (%)	Class of recommendation
Patients with symptomatic HF (NYHA class II or III), ischemic cause, more than 40-day post-MI, on adequate medical therapy	≤35	I
Patient with symptomatic HF (NYHA class II or III), non-ischemic cause, on adequate medical therapy	≤35	I
Patient with LV dysfunction secondary to MI, asymptomatic (NYHA class I) more than 40-day post-MI, on adequate medical therapy	≤30	I
Patient with non-sustained VT due to prior MI with inducible VF or sustained VT at electrophysiology study	≤40	I
Patient with asymptomatic (NYHA class I) non-ischemic cardiomyopathy	≤35	IIb

LVEF, Left ventricular ejection fraction; *ICD*, implantable cardioverter defibrillator; *HF*, heart failure; *MI*, myocardial infarction; *LV*, left ventricle; *VT*, ventricular tachycardia; *VF*, ventricular fibrillation.

patient survival with revascularization or medical therapy, LVEF remained the strongest predictor for cardiac death, while ischemia was a better predictor for revascularization benefit (Figure 1). Lertsburapa et al, in a study with 1441 patients undergoing PET MPI with Rubidium-82 chloride, demonstrated that LVEF measured on the ECG-gated images was an independent and incremental prognostic marker. Annualized mortality rates in the group with LVEF above 50%, between 40% and 49%, and below 40% were, respectively, 2.4%, 6.2%, and 9.2% ($P < .001$).[33] Curtis et al, in a study with 7788 patients with known HF, demonstrated similar results using RNA. In their study, over a mean follow-up of 37 months, they demonstrated that mortality increased in a near linear fashion with decreasing LVEF below 45%, while mortality rates were not related to LVEF above 45%.[26]

RNA is a particularly useful and powerful tool for the evaluation of LVEF and is an integral part of current imaging guidelines and appropriate use criteria documents[34,35] (Table 3). Along with cardiac magnetic resonance (CMR), it is currently one of the most accurate and reliable modalities for LVEF measurement and has excellent inter- and intraobserver reproducibility.[36-39] Its advantages and disadvantages are summarized in Table 4. Even though LVEF measurement is not enough by itself to accurately predict SCD,[10] it remains a strong and important key parameter in current practice and guidelines. Nuclear cardiology offers varied and accurate means to evaluate it.

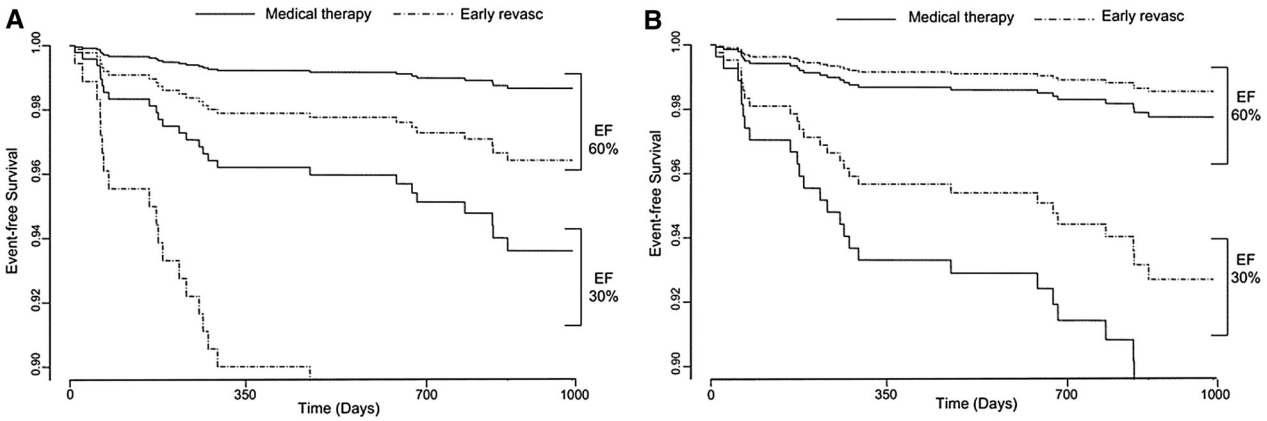

Figure 1. Survival free of cardiac death in patients without ischemia (**A**) and patients with a minimum of 25% ischemic myocardium (**B**) undergoing either revascularization or optimal medical therapy, stratified by LVEF. Reproduced with permission from *J Nucl Cardiol*®[32].

Table 3. Class I indications for RNA

LV function evaluation—risk, prognosis, and therapy assessment
STEMI
Unstable angina
NSTEMI
Assessment of LV/RV function
Heart failure
CAD
Valvular heart disease
Congenital heart disease
Assessment of ventricular performance following cardiac transplantation
Initial and serial assessment of LV function in patient receiving cardiotoxic drugs

RNA, Radionuclide angiography; *STEMI*, ST segment elevation myocardial infarction; *NSTEMI*, non-ST segment elevation myocardial infarction; *LV*, left ventricle; *RV*, right ventricle; *CAD*, coronary artery disease.

Table 4. RNA advantages and disadvantages compared to CMR

Advantages
Excellent temporal resolution
No geometric assumptions
Less affected by body habitus
No device contra-indication
Not time consuming (imaging requires less than 30 minutes)
Disadvantages
Poor spatial resolution
Limited anatomic assessment of cardiac chambers
Ionizing radiation
Limited assessment of smaller area of regional wall motion abnormalities

RNA, Radionuclide angiography; *CMR*, cardiac magnetic resonance.

ISCHEMIA

Ischemia is a well-recognized trigger for ventricular arrhythmias.[40,41] Current ICD therapy guidelines recommend optimal revascularization before ICD therapy.[31] Moreover, coronary revascularization has been proven to reduce SCD risk.[42-44] Hachamovitch et al, in a large study with 5183 patients who underwent rest/stress dual-isotope (Thallium-201 and Technetium-99m Sestamibi) SPECT MPI, demonstrated that the presence of ischemia yields incremental prognostic data for predicting cardiac death and adverse cardiac events.[45] Annual rates of cardiac death increased with increasingly abnormal MPI going from 0.5% in patients with normal scans to 4.2% in patients with severely abnormal MPI (defined as a sum stress score (SSS) of more than 13).[45] More recently, Piccini et al, in a study of 6383 patients with angiographically documented CAD, investigated if ischemia on SPECT MPI was a predictor for cardiac death and more specifically for SCD.[46] In their final multivariable analysis, the SSS was a significant predictor for SCD, with a hazard ratio of 1.16 per 3-U increase (95% CI 1.08-1.25). The ability of the SSS to predict SCD was comparable to that of LVEF. Interestingly, in the same multivariable analysis, neither the sum rest score (SRS, which reflects scar), nor the sum difference score (SDS, which reflects ischemia), were statistically significant predictors for SCD. Taken together, this implies that it is the combination of scar and ischemia that has the strongest predictive value for SCD, which matches well with our current understanding of SCD mechanisms. Another interesting fact from this study is that the median LVEF of patients who experienced SCD was 47%, again underscoring the lack of sensitivity of simple LVEF measurement in predicting SCD. Furthering this point, in a follow-up study Piccini et al demonstrated that their previous finding held true in a group of 4865 patients, all of whom had LVEF $> 35\%$ (median LVEF 56%)[47] (Figure 2). In another study, Paganelli et al studied the effect of residual ischemia in patients with prior myocardial infarction. Using programmed ventricular stimulation, they demonstrated that residual ischemia on SPECT MPI carried a 1.6-fold increase in the risk of inducible ventricular arrhythmias.[48]

Although there is less data regarding PET MPI as a predictor for SCD, recent meta-analyses have shown that PET MPI is superior to SPECT MPI in the detection of CAD.[49,50] Its prognostic value is well established.[51] Data from a recently completed multicenter registry show an increasing risk of cardiac events and cardiac death in patient with increasingly abnormal stress PET MPI,[52] although the authors did not look specifically at SCD. It would appear to be a safe assumption that ischemia as evidenced by PET MPI can play a role similar to SPECT MPI in the prediction and management of SCD, although this will need to be studied further to determine if there is an advantage over SPECT MPI.

In addition, PET MPI permits accurate and reproducible measurement of myocardial blood flow (MBF) at both rest and stress.[53] In a recently published paper, Rijnierse et al demonstrated that in patients with ischemic cardiomyopathy, impaired hyperemic MBF and impaired coronary flow reserve (CFR, stress MBF/

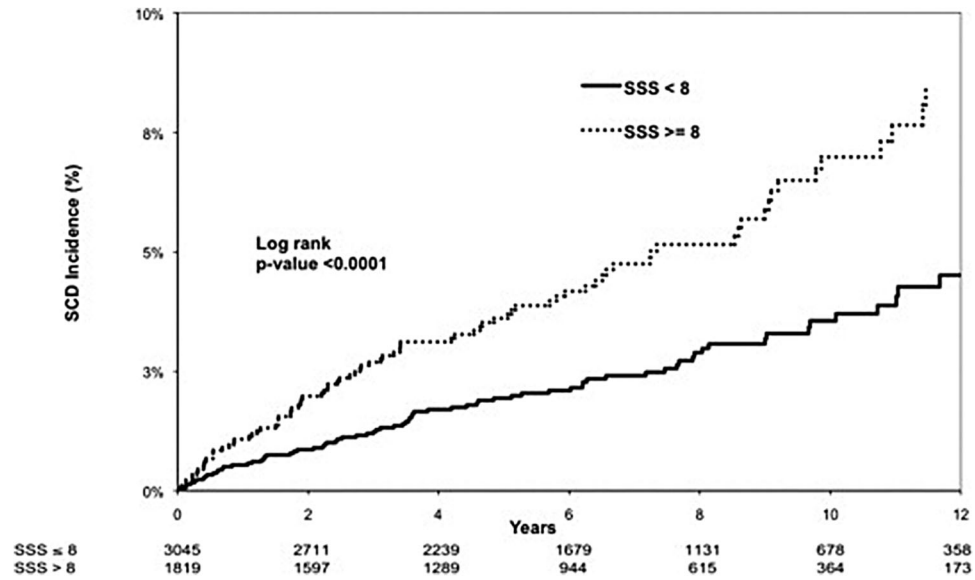

Figure 2. Cumulative incidence of sudden cardiac death in patients with summed stress score ≤8 vs >8. Reproduced with permission from *JACC*[47].

rest MBF), whether in scar area or remote area, were associated with increased ventricular arrhythmia inducibility during electrophysiological evaluation.[54] These results suggest a link between impaired stress MBF and electrical instability, and a potential benefit of PET MPI to help accurately stratify patients at risk for SCD.

MYOCARDIAL SCAR AND HIBERNATING MYOCARDIUM

Myocardial scar is a complex and powerful substrate for arrhythmogenesis. Changes in tissue composition following an infarct create a heterogeneous zone that leads to depolarization abnormalities, autonomic dysfunction, and repolarization disruption; the presence of viable myocardium adjacent to scar tissue often forms the anatomic substrate for reentrant ventricular tachycardia (VT).[55,56] Studies have shown that the extent of scar on SPECT MPI is related to the risk of cardiac death. Machecourt et al studied 1926 patients using SPECT MPI and demonstrated that persistent rest and stress imaging defects (scar) were associated with increased cardiovascular death, and that the greater the number of abnormal segments, the worse the prognosis.[57] Van der Burg et al studied SCD survivors using SPECT MPI and demonstrated that the presence of more extensive scar was associated with greater risk for recurrent ventricular arrhythmias and cardiac death in both the univariate and multivariate analysis.[44] In another study with 106 patients with LVEF ≤ 30%, Morishima et al showed that defect size on rest SPECT MPI (representing scar) was a predictor for lethal arrhythmic events and SCD.[58] Using a threshold value of 47.5 mL for defect volume (determined using ROC curve analysis), the risk ratio was 6.34 (95% CI 1.76-22.8, $P = .005$). This illustrates how, in clinical practice, assessing the extent of scar might help better and more accurately assess SCD risk.

Furthermore, the assessment of hibernating myocardium in current clinical practice is well established. Hibernating myocardium is identified using a combination of metabolic imaging (Fluorine-18 fluorodeoxyglucose (^{18}F-FDG)) and myocardial perfusion (generally Rubidium-82 chloride (^{82}Rb) or Nitrogen-13 ammonia ($^{13}NH_3$)) and will present with a perfusion defect with maintained or even enhanced glucose metabolism (Figure 3). While PET is preferable, in centers which do not have access to PET, it is possible to evaluate hibernating myocardium using SPECT (either with Thallium-201 or Technetium-99m Sestamibi). Viable myocardium is known to represent an unstable electrical region, and it is associated with an increased risk for SCD.[59] A study by Di Carli et al looked at 93 patients undergoing PET MPI with $^{13}NH_3$ and viability assessment with ^{18}F-FDG.[60] They showed that an increased perfusion-metabolism mismatch (hibernating myocardium) was associated with an increased cardiac death risk. Patients with at least 5% hibernating myocardium had much lowered annual survival probability than those without (50% vs 92%, $P = .007$) and were also shown to benefit from

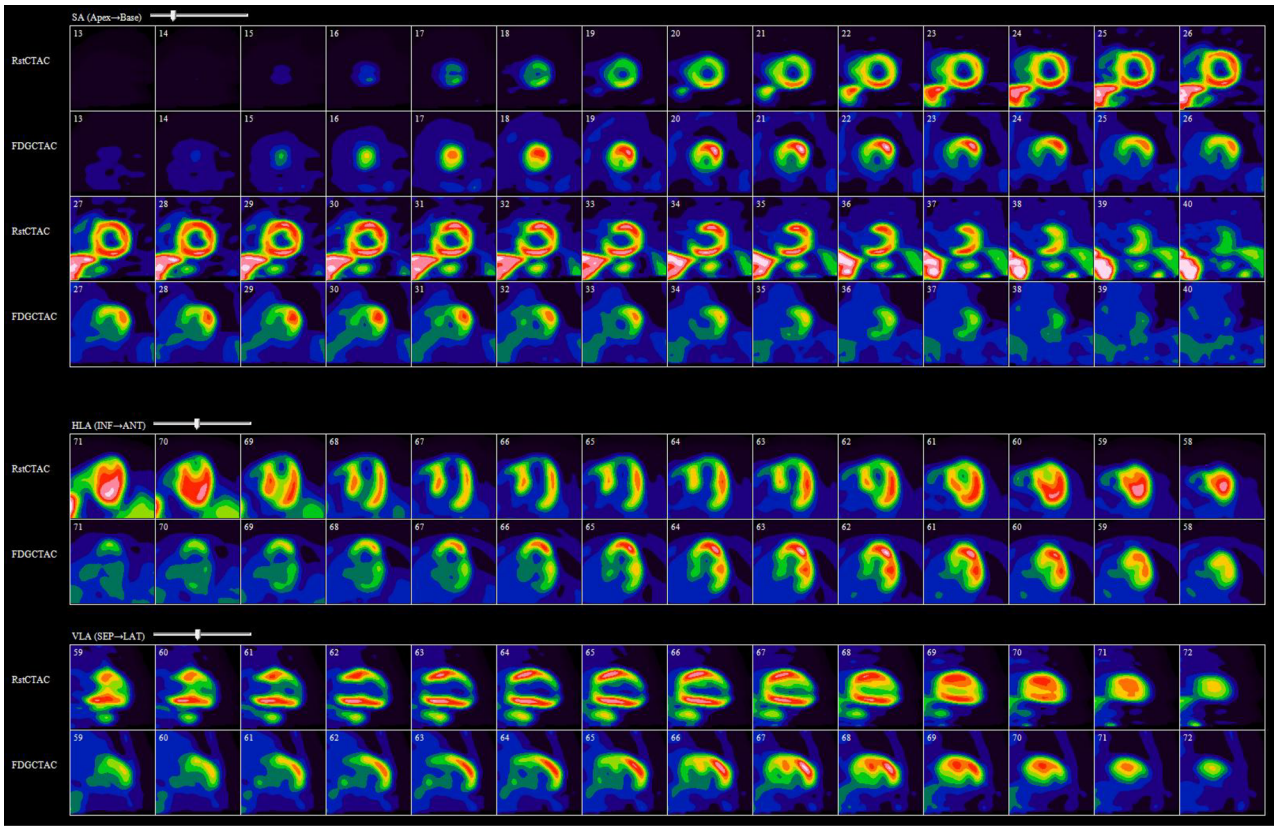

Figure 3. Viability study demonstrating a large area of hibernating myocardium in the LAD territory. Rest PET perfusion imaging using ^{13}N-NH_3 (*upper row*) shows a moderate reduction in perfusion in the distal anterior, antero-septal, and septal walls as well as the apex. ^{18}F-FDG PET (*bottom row*) shows a corresponding area of increased glucose metabolism in the same territory.

revascularization rather than medical therapy.[60] Similar results were obtained by Desideri et al, who observed that in 167 patients being treated medically, the extent of hibernating myocardium was strongly related to cardiac mortality ($P = .001$).[61] An 8% increase in mismatch was associated with a 36% increase in cardiac mortality (HR 1.36, 95% CI 1.13 to 1.64). More recently, the PET and Recovery Following Revascularization (PARR-2) trial, a large randomized trial, investigated whether viability imaging with ^{18}F-FDG PET could be used to effectively assist decision making in patients with severe LV dysfunction to reduce cardiac events and cardiac death.[62] While the primary study did not demonstrate a clear benefit, a post hoc analysis demonstrated that when PET recommendations were adhered to, a benefit was observed in patients with significant hibernating myocardium, with a hazard ratio of 0.62 for cardiac events (95% CI 0.42-0.93, $P = .019$).[62] Ling et al and Uebleis et al, in separate studies, obtained similar results in patients with ischemic cardiomyopathy and LV dysfunction.[63,64] Not all studies have demonstrated similar results. In a substudy of the Surgical Treatment for Ischemic Heart Failure (STICH) trial,[65] the presence of viable myocardium was not significantly associated with an improved outcome in the final adjusted analysis. However, it should be noted that in this substudy, viability was assessed using either SPECT or dobutamine echography instead of PET, and that the criteria for classifying myocardium as viable or non-viable did not include wall motion information (in contrast to earlier studies in which viability was assessed only in dysfunctional regions). As well, it is interesting to note the patients were selected from a group already well suited to revascularization and that their population suffered from less comorbidity then what is reported in other studies.[66]

In practice, defining the extent of ischemia, hibernation, and scar is an important step in the work up of patients with SCD and/or ventricular arrhythmia. In light of the possible reversibility of ischemia and hibernating myocardium-induced arrhythmias, accurate evaluation of these conditions appears necessary, a goal which can be achieved using SPECT and PET imaging. Even in cases where revascularization is not possible, the extent

of ischemia and hibernation as well as the extent of scar should be taken into account when considering primary prevention for SCD.

SYMPATHETIC INNERVATION IMAGING

Cardiac sympathetic innervation is another novel imaging target in the search for better prediction and prevention of SCD. It plays an important role in cardiac function and may play an important role in future stratification strategies.

The most widely available and studied non-invasive method to assess cardiac sympathetic innervation is currently Iodine-123-metaiodobenzylguanidine (MIBG). MIBG is a guanethidine analog initially developed in the 1980s to study adrenal medulla tumors and other neuroendocrine tumors.[67] It mimics norepinephrine (NE), the main neurotransmitter involved in the sympathetic innervation of the heart. It localizes mainly in presynaptic nerve endings, which it enters by an active energy-dependent transport (uptake 1) before being stored in neurosecretory granules. However, unlike NE, it is not metabolized by monoamine oxidase, which allows it to accumulate in sufficient concentration to permit imaging.[68] Cardiac imaging with MIBG is done using a standard gamma camera, with images acquired both in planar views and SPECT 15 minutes after tracer injection, and again 3-5 hours after tracer injection.[69] Planar images are then used to calculate the heart-to-mediastinum ratio (H/M ratio) and the cardiac washout of the tracer between the early (15 minutes) and delayed images (3-5 hours), while SPECT images are used mainly to assess for regional uptake and defects.

Both animal and human models have shown that sympathetic innervation anomalies are associated with ventricular arrhythmias.[23,70,71] These anomalies also play an important role in HF and can be associated with worsening LV function and symptoms, as well as an increase in SCD.[72] Bax et al demonstrated an association between MIBG defect severity and inducibility of VT in electrophysiology studies.[73] The AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) trial, a prospective study with 961 patients with NYHA class II or III HF and LVEF $\leq$ 35%, is one of the largest studies that have looked at cardiac MIBG imaging and its prognostic value.[74,75] For H/M $<$ 1.60, cardiac death at 2 years was 11.2% vs 1.8% for the group with H/M $\geq$ 1.60[74] (Figure 4). When treated as a continuous variable, over a median follow-up of 17 months, there was a progressive decline in cardiac death from 20% for H/M $<$ 1.10 to 0% for H/M $>$ 1.80[74] (Figure 5). Lastly, the risk of arrhythmic event was significantly higher in patient with H/M $<$ 1.60 vs patients with H/M $\geq$ 1.60 (10.4% vs 3.5%, $P < .001$).[74] These results were further supported by a follow-up analysis in the ADMIRE-HF extension study (ADMIRE-HFX) whose results were recently published.[76] In another interesting study, Boogers et al investigated the ability of cardiac MIBG imaging to predict ventricular arrhythmias in patients with ICD. They prospectively recruited 116 HF patient referred for ICD therapy, who all underwent cardiac MIBG SPECT before ICD implantation. Over a follow-up of approximately 2 years, they showed that large defects on late MIBG SPECT imaging were strongly associated with ventricular arrhythmias and appropriate ICD therapy when compared with patients with no or small defects (52% vs 5%, $P < .01$).[77] A similar study by Kawai et al investigated the ability of MIBG to identify patients with HF and reduced LVEF but at low risk for SCD.[78] They recruited 81 patients with stable HF and LVEF $\leq$ 35%, who were then followed-up for a minimum of 5 years. At recruitment, every patient underwent cardiac MIBG and the authors combined

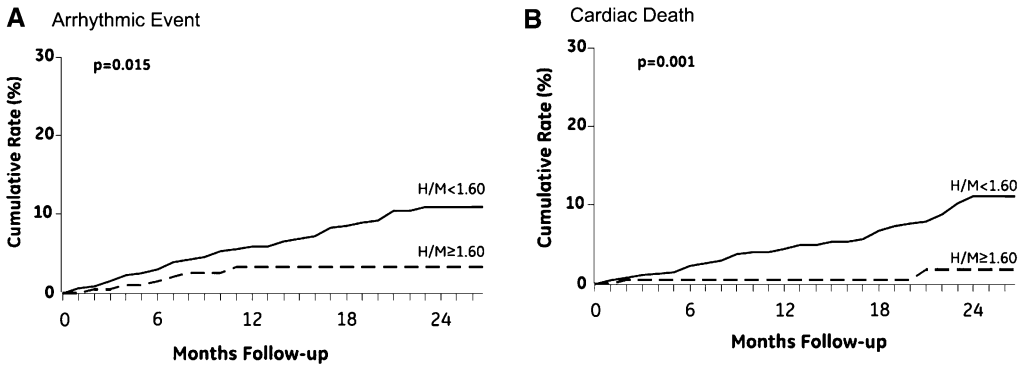

Figure 4. Cumulative event curves for arrhythmic events (**A**) and cardiac death (**B**) in patients with MIBG heart-to-mediastinum ratio <1.60 vs patient with ratio ≥1.60. Adapted with permission from *JACC*[74].

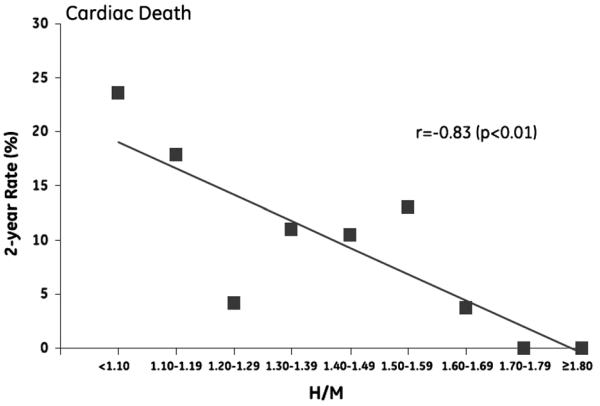

Figure 5. Cumulative two-year cardiac death rate vs MIBG heart-to-mediastinum ratio. Reproduced with permission from *JACC*[74].

the H/M ratio and washout rate to calculate a MIBG score ranging from 1 (normal) to 10 (highly abnormal). The patients were thus stratified into low (1-4), intermediate (5-7), and high (8-10) MIBG scores. This score proved to be a strong predictor for SCD (low = 0%, intermediate = 19%, and high = 36%, $P = .001$). The positive predictive value of a low MIBG score to identify patients at low risk for SCD was thus 100%. As the authors pointed out, an interesting aspect of their study is that they combined both the H/M ratio and washout rate in one score. We know that these parameters, although they overlap, do not represent the exact same phenomenon, and the authors postulated that combining them might further enhance the predictive value of MIBG.[78]

While many studies investigating the role of cardiac MIBG imaging looked at patient with severely reduced LVEF, other studies have also validated its prognostic value in patients with normal or near-normal LVEF.[79,80] A high MIBG washout rate is also associated with increased risk for SCD.[81] Other authors have also looked at the link between hibernating myocardium and sympathetic innervation. We know that the nerve endings are more sensitive to ischemia than the myocardial cells, and it is thus not surprising that studies in animal models and human subjects have shown that area of mismatched innervation/perfusion (abnormal innervation but preserved perfusion) are arrythmogenic.[82-84]

PET technology has many intrinsic advantages over SPECT and has become more readily available over the last 10 years, which has led to an increase in research regarding PET imaging of cardiac innervation and the autonomic nervous system using PET norepinephrine analogs including ^{11}C-HED (Carbon-11-*meta*-hydroxyephedrine), Carbon-11-epinephrine, and beta receptor ligands such as C-11-CGP-12177. These tracers have been used to understand the role of the sympathetic nervous system in cardiomyopathy pathogenesis and the effects of therapy.[85] The most investigated of these PET tracers is ^{11}C-HED. Its uptake and storage is similar to that of MIBG, but it has a higher uptake 1 selectivity.[86] With the background of (i) persistent innervation damage in patients with previous myocardial infarction and hibernating myocardium,[87-90] (ii) the association between MIBG uptake and SCD as per Boogers et al,[77] (iii) prior studies suggesting low^{11} C-HED retention predicts adverse outcomes[91] and (iv) that as strong a predictor as LVEF is, we remain unable to better stratify patients for consideration of ICD therapy,[13] Fallavollita et al designed the Prediction of ARrythmic Events With Positron Emission Tomography (PAREPET) trial. In a prospective study, they recruited 204 patients with LVEF $\leq$ 35%, eligible for primary prevention ICD therapy. Their aim was to demonstrate an association between the amount of myocardial sympathetic innervation anomalies and the risk of SCD. All patients had ^{18}F-FDG PET for viability assessment and ^{11}C-HED PET for myocardial innervation assessment and quantification.[92] The volume of denervated myocardium as a continuous value was a strong independent predictor of SCD and had the strongest correlation with SCD, with a HR of 1.069 per 1% of LV (95% CI 1.023-1.117, $P = .003$). The volume of viable, denervated myocardium was also a strong predictor for SCD as a continuous value, with a HR of 1.067 per 1% of LV (95% CI 1.008-1.130, $P = .025$). When divided by tertiles of sympathetic denervation, the patients in the highest tertile had the highest rate of SCD, while the patients in the lowest tertile had the lowest rate (6.7, 2.2 and 1.2%·year^{-1}, respectively), with a statistically significant difference between all tertiles (Figure 6).

When comparing MIBG and ^{11}C-HED in animals and humans, some studies have reported good correlation between the two,[93] while others reported significant differences, with ^{11}C-HED defect being larger than MIBG defects.[94] Some data also support the theory that ^{11}C-HED provides a better signal-to-noise ratio,[90,95] likely explained by the better imaging characteristics of PET, its higher sensitivity, and the higher specificity of ^{11}C-HED for NE uptake 1. However, the short half-life (20 minutes) of ^{11}C-HED has limited its availability to centers with onsite cyclotron.

In clinical practice, the presence and extent of either global or regional cardiac sympathetic denervation or anomalies should be taken into account when considering ICD therapy if it is available. The current data support a more aggressive approach toward ICD therapy in patient with more extensive or severe sympathetic innervation anomalies, even in patients with normal or

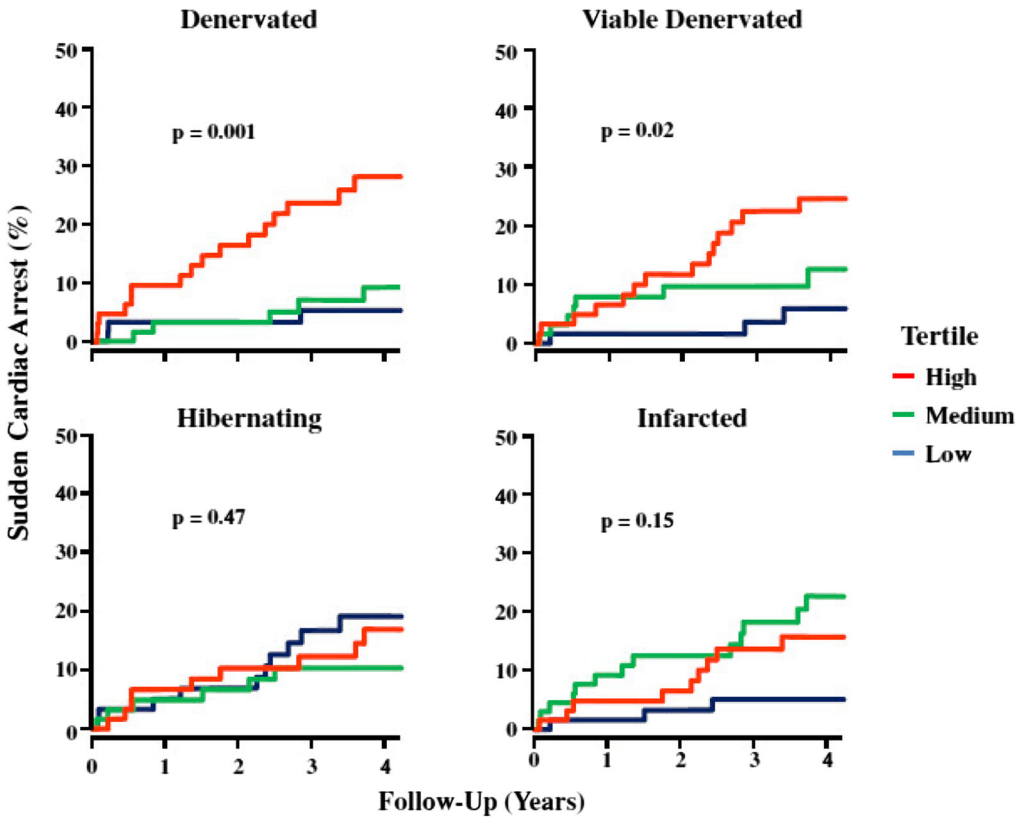

Figure 6. Kaplan-Meier curves showing the relationship between the extent of four different PET-defined myocardial substrates (as continuous variable) and sudden cardiac death: *1* denervated (reduced Carbon-11-*meta*-hydroxyephedrine (HED) uptake), *2* hibernating (reduced perfusion/maintained Fluorine-18 fluorodeoxyglucose (FDG) mismatch), *3* viable denervated (reduced HED/maintained FDG mismatch), and *4* infarcted (reduced perfusion/FDG match). The total volume of denervated and viable denervated myocardium are both significant predictors for sudden cardiac death. Reproduced with permission from *JACC*[92].

near-normal LVEF values, although this has not yet been adopted into practice guidelines.

SPECIFIC CARDIOMYOPATHY CONDITIONS

Idiopathic Dilated Cardiomyopathy (DCM)

According to some studies, SCD accounts for up to 30% of overall death in patients with DCM,[96] which accounts for a significant fraction of overall SCD.[6] Current guidelines recommend ICD therapy in patients with non-ischemic cardiomyopathy with LVEF $\leq$ 35% and NYHA class II-III HF,[29] while it may be considered in patients with NYHA class I. Evaluation of LV function is thus indicated in these patients. Additionally, studies have shown that sympathetic innervation abnormalities are present in DCM. Kasama et al, in a study involving 56 patient with DCM, showed that patients with reduced H/M ratio and increased washout rate on MIBG imaging had significantly more late ventricular potentials on signal averaged ECG and were thus at higher risk for SCD.[97] Over the average follow-up time of 4.5 years, both the H/M ratio and washout rate were significant predictors for SCD ($P = .004$ and $P = .002$ respectively). Other studies have shown similar results, supporting the prognostic role of cardiac sympathetic innervation in DCM.[98] Recent studies have also looked at the presence of significant microvascular dysfunction in patients with DCM.[99,100] In a study with 510 patients, Majmudar et al investigated the relationship between CFR and major adverse cardiac events (MACE, including cardiac death, SCD, and aborted SCD) in patients with ischemic and non-ischemic cardiomyopathy and LVEF $\leq$ 45%.[100] Reduced CFR was common in both ischemic and non-ischemic cardiomyopathy and was a significant predictor for MACE, with a 32.6%/year rate in the group with CFR $\leq$ 1.65 and a 15.5%·year^{-1} rate in the group with CFR $>$ 1.65 ($P = .004$).[100] Although the exact mechanism underlying the reduced CFR in patients with non-ischemic cardiomyopathy is still

unclear, another recent study by Rijnierse et al showed that there was a significant association between hyperemic MBF and sympathetic innervation.[101] In 70 patients with ischemic cardiomyopathy or DCM, they showed that ^{11}C-HED retention was correlated with resting MBF ($r = 0.041$, $P < .001$) and hyperemic MBF ($r = 0.055$, $P < .001$) as assessed by Oxygen-15-water PET in non-infarcted myocardium. Whether this is causative or not remains to be determined.

Hypertrophic Cardiomyopathy (HCM)

HCM is a heterogeneous disease with varying presentation and expression, which represents the most common cause of SCD in adults younger than 40 years.[29] ICD therapy has been shown to be appropriate in patients with HCM and risk factors for SCD and is part of current guidelines.[102,103] Nuclear cardiology can play a role in these patients by evaluating myocardial ischemia, which is known to be an important determinant of the clinical course of HCM.[104] In a study of 158 patients with HCM, more than half had abnormal SPECT MPI, and the SSS was significantly associated with cardiovascular death. Patients with a low, intermediate, and high SSS had a 5-year survival of 97%, 94%, and 79%, respectively, ($P = .04$), and the presence of ischemia was a predictor of cardiovascular death (HR 1.77, 95% CI 1.04-3.02, $P = .04$) in the final multivariate analysis.[104] Microvascular dysfunction is also known to be a feature of HCM.[105] Cecchi et al showed using $^{13}NH_3$ PET that patients with HCM had a severely diminished vasodilator response to dipyridamole when compared with a control group (hyperemic MBF 1.50 ± 0.69 vs 2.71 ± 0.94 mL·g^{-1}·minute^{-1}, $P < .001$), while resting flow was similar in both groups.[105] In addition, in the HCM group, a lower hyperemic MBF was associated with an increased risk of cardiac death.

Some authors have validated the usefulness of sympathetic innervation imaging in patients with HCM.[106-108] Terai et al studied the link between cardiac sympathetic innervation and ventricular arrhythmias using MIBG. Patients who experienced ventricular tachy-arrhythmias had a significantly higher MIBG washout rate ($26.8 \pm 6.4\%$ vs $17.4 \pm 5.7\%$, $P < .001$),[108] supporting the hypothesis that cardiac innervation imaging can help identify HCM patients at higher risk for SCD.

Cardiac Amyloidosis

Amyloidosis is a rare disease marked by the abnormal deposition of amyloid, which is basically inappropriately folded protein. Depending on the type of protein involved, there are four main types of amyloid (AL, AA, ATTR, and AB2M), and the disease can be systemic or restricted to one organ in some cases.

Cardiac involvement is not uncommon and is one of the main determinants of prognosis, and can result in high-degree heart block, severe biventricular dysfunction, and SCD.[109-111] Current guidelines support the use of ICD in patients with cardiac involvement and ventricular arrhythmia causing hemodynamic instability.[9] Studies have shown that cardiac sympathetic innervation abnormalities are frequently present in patients with cardiac amyloidosis and are often more pronounced in patients with associated HF.[112] To our knowledge, no study has specifically investigated the link between sympathetic innervation abnormalities and SCD in this population, but since such a link exists in other populations, we anticipate it translates to this one. The exact role of nuclear cardiology in this disease remains to be determined, but small studies and case reports have shown that both SPECT (using bone agents such as Technetium-99m-pyrophosphate) and PET (using amyloid seeking tracers such as Carbon-11 Pittsburgh compound B and Fluorine-18-florbetapir) can potentially be used to establish the diagnosis of cardiac involvement in amyloidosis.[113,114]

Cardiac Sarcoidosis (CS) and Other Inflammatory Cardiomyopathies

Sarcoidosis is a systemic inflammatory disease characterized by the formation of noncaseating granulomas. The exact etiology remains unknown, and the disease can involve nearly any organ, although the lungs and lymph nodes are by far the most commonly involved. Cardiac involvement can lead to conduction disturbances, ventricular arrhythmias, HF, and SCD. The exact prevalence of myocardial involvement remains controversial, ranging anywhere from 2% to 40%.[115,116] Patients with cardiac involvement are often asymptomatic and initial presentation can range from asymptomatic to SCD or ventricular arrhythmia. In a study by Nery et al, 182 patients presenting with new onset unexplained monomorphic VT underwent comprehensive investigation including ^{18}F-FDG PET. 42% had findings suggestive of CS, underlining the importance of screening for CS.[117] Similarly, a significant proportion of patients presenting with unexplained new onset atrioventricular block turn out to have CS.[118,119] SCD secondary to arrhythmias is the cause of death in up to 50% of all sarcoidosis deaths, with some studies reporting even higher numbers.[120] The diagnosis of cardiac involvement remains challenging, but cardiac magnetic resonance and cardiac PET are emerging as pivotal tools in its assessment.[121] Assessment for CS

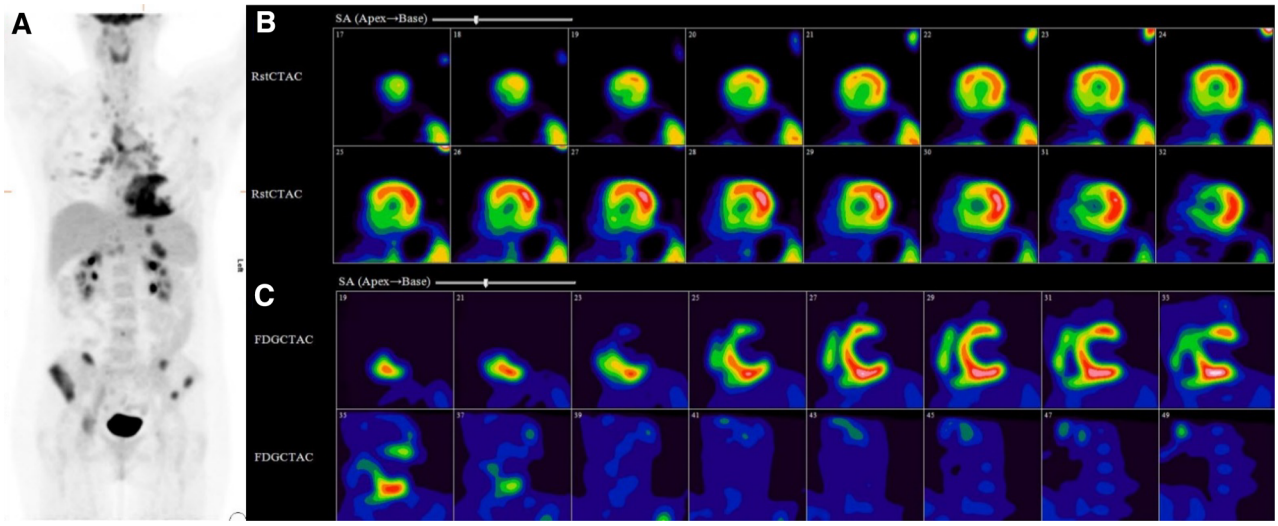

Figure 7. This otherwise healthy 57-year-old female presented with new onset complete heart block and no pertinent prior medical history. Echocardiogram was normal, including normal LVEF. Because there was a suspicion for sarcoidosis, she underwent ^{18}F-FDG PET-CT. Wholebody ^{18}F-FDG PET (**A**) images revealed extensive active systemic sarcoid, with active lesions in the lungs, nodes, spleen, and bones. Cardiac involvement was present. ^{82}Rb MPI PET revealed areas of decreased perfusion mainly in the septum and inferior walls (**B**) while dedicated ECG-gated ^{18}F-FDG myocardial acquisition (**C**) revealed areas of severely increased uptake in the septal, anterior, and inferior walls. The decision was taken to go ahead with implantable cardioverter defibrillator (ICD) implantation. The patient received appropriate, life-saving shock 10 months later for ventricular fibrillation arrest.

using nuclear cardiology requires two different image acquisitions: one assessing perfusion (which can be done using either SPECT or PET) and ^{18}F-FDG PET to assess for active inflammation. Active CS will classically appear as a focal area of reduced or absent perfusion with increased ^{18}F-FDG uptake.

In the largest study of its kind to date, Blankstein et al studied the prognostic value PET in CS.[122] They followed 118 patients with known or suspected CS over a median of 1.5 years. The patients who had scans suggestive of CS at presentation (perfusion defect with associated increased ^{18}F-FDG uptake) were at a significantly increased risk for death or ventricular tachycardia in the final multivariate analysis (HR 2.87, $P = .039$).

According to the recent HRS consensus statement, ICD is recommended in patients with cardiac sarcoidosis and ventricular arrhythmias or high-degree heart block[123]—a position supported by the literature[124-126] (Figure 7).

Lastly, a recent paper by Tung et al looked at the incidence of abnormal myocardial ^{18}F-FDG uptake in patients with otherwise unexplained cardiomyopathy referred for ventricular arrhythmias. Out of 103 patients recruited, 50 (49%) were found to have abnormal focal myocardial ^{18}F-FDG uptake, consistent with an active myocardial inflammatory process.[127] This impacted therapy in nearly all of these patients, most of which went on to receive immunosuppressive therapy or underwent ablation.

Other Conditions

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically inherited cardiomyopathy which can cause ventricular arrhythmia and SCD. One group has shown that cardiac sympathetic innervation abnormalities are frequently present in these patients, using both MIBG,^{11}C-HED PET, and ^{11}C-CGP-12177 (a marker of post synaptic beta-adrenergic receptors).[128,129] They reported the presence of regionally reduced MIBG uptake in 40/48 patients with ARVC, and these areas of abnormal sympathetic innervation were strongly correlated with the site of origin of ventricular tachycardia in patients with right ventricular outflow tract tachycardia.[128] In a follow-up study with 42 ARVC patients followed for more than 10 years, they demonstrated that the patients with abnormal MIBG scans were at a significantly increased risk to develop life-threatening VT vs those with normal sympathetic function (88% vs 35% over total follow-up, $P < .0005$).[130]

Some evidence also supports a role for cardiac sympathetic innervation imaging in Brugada syndrome,

another cause of SCD. Wichter et al demonstrated that regionally decreased MIBG was present in nearly 50% of patients with Brugada syndrome,[131] while Kies et al demonstrated that they have abnormal uptake of ^{11}C-HED on PET.[132] This, combined with clinical evidence of autonomic nervous system dysfunction,[133] supports the hypothesis of autonomic dysfunction in Brugada syndrome's pathophysiology, but whether or not it has any prognostic value and can help in clinical decision-making remains to be determined.

FUTURE OUTLOOK

Although ^{11}C-HED shows great promise, its use and adoption remain limited because of its short half-life which requires an onsite cyclotron. LMI1195 is a Fluorine-18-based PET tracer with a design similar to MIBG, which could theoretically solve this problem thanks to its longer half-life which allows delivery from a regional cyclotron. Preliminary studies are promising,[134,135] and the relationship between myocardial denervation and SCD, along with the potential for an effective Fluorine-18-labeled tracer suggest the potential for LMI1195 to help identify high-risk patients for SCD and guide ICD therapy.

The ability of PET to detect picomolar levels of radiotracers could also eventually lead to imaging of channelopathies, something currently impossible, although appropriate tracers would first have to be developed. Potential applications for PET/MRI hybrid scanners in the field of SCD are numerous. Cardiac magnetic resonance is currently the clinical gold standard in evaluating ventricular function and can accurately assess scar tissue. Combining this data with the functional and physiological data acquired using PET could potentially lead to a better understanding of the underlying mechanism and physiopathology of SCD, and ultimately better risk stratification.

Lastly, it should be noted that further studies evaluating the etiology, outcome, and directing therapy specifically in SCD are required, as some of the data we currently rely on only uses cardiac death, rather than SCD, as an endpoint.

CONCLUSION

Correctly identifying patients who are at high risk for SCD is of paramount importance since appropriate therapy can be life-saving. While modern medicine has made significant progress in the diagnosis and management of CAD, this is one area where recent progress remains limited. Our current screening process for SCD relies heavily on LVEF assessment, which lacks both sensitivity and specificity. Recent advances in our understanding of the underlying pathophysiology, combined with advances in cardiac imaging, offers hope for a new and better predictive model. Imaging of ischemia, scar tissue, hibernating myocardium, and cardiac innervation all seem to hold the potential to identify additional high-risk features for SCD in patient with or without LV dysfunction. Further validation with large prospective studies will be needed to validate these new risk predictors before they can be widely adopted in the clinical setting and integrated in an improved everyday model of SCD risk prediction that will more accurately guide clinicians in decision-making. Hopefully, this will lead to appropriate ICD therapy in patients in whom it would previously not have been indicated, as well as reduced ''inappropriate'' ICD therapy in patients with low LVEF who never experience ventricular arrhythmia or SCD.

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