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Prognostic Significance of Imaging Myocardial Sympathetic Innervation

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Abstract

There has been a longstanding interest in understanding whether the presence of inhomogeneity in myocardial sympathetic innervation can predict patients at risk of sudden cardiac arrest from lethal ventricular arrhythmias. The advent of radiolabeled norepinephrine analogs has allowed this to be imaged in patients with ischemic and non-ischemic cardiomyopathy using single, photon emission computed tomography (SPECT) and positron emission tomography (PET). Several observational studies have demonstrated that globally elevated myocardial sympathetic tone (as reflected by reduced myocardial norepinephrine analog uptake) can predict composite cardiac end-points including total cardiovascular mortality. More recent studies have indicated that quantifying the extent of regional denervation can predict the risk of lethal ventricular arrhythmias and sudden cardiac death. This review will summarize our current understanding of the prognostic significance of altered myocardial sympathetic innervation.

Keywords

Myocardial sympathetic innervation; ^{131}I-meta-iodo-benzyguanidine; ^{11}C-hydroxyephedrine; Sudden cardiac death; Regional denervation; Myocardial infarction; Hibernating myocardium

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Compliance with Ethics Guidelines

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Alterations in cardiac sympathetic activity have been linked to disease progression and increased mortality in cardiovascular disease [1••]. The clinical manifestations of cardiac sympathetic dysfunction are frequently subtle and may manifest as alterations in resting heart rate, heart rate variability, or impairment of cardiac autonomic reflexes such as blunting of the chronotropic response to changes in systemic hemodynamics. For the past several decades, compelling preclinical data has accumulated demonstrating a link between cardiac sympathetic nerve activity and ventricular arrhythmias leading to sudden cardiac death (SCD) [2]. This review will focus on imaging myocardial sympathetic innervation in patients with ischemic cardiomyopathy and review studies suggesting that it may help to better identify patients at risk for SCD.

Left Ventricular Dysfunction and Sudden Cardiac Death

Advances in coronary revascularization and the advent of highly potent pharmacological agents for the treatment of acute coronary syndromes have improved overall survival but increased the prevalence ischemic cardiomyopathy and heart failure as consequences of coronary artery disease. The development of ischemic cardiomyopathy is accompanied by dynamic myocyte and neuronal remodeling that exacerbates the risk for SCD from lethal ventricular arrhythmias. For example, the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) found patients with ischemic cardiomyopathy and reduced left ventricular ejection fraction (LVEF; <30 %) to have an all-cause mortality approaching 20 % during an average follow-up period of 20 months [3]. Prophylactic insertion of an implantable cardiac defibrillator (ICD) reduced absolute risk by 5.6 %. Similar findings were demonstrated in the Sudden Cardiac Death in Heart Failure (SCD-HeFT) trial which also found no effect of prophylactic antiarrhythmic therapy with amiodarone on survival [4]. Although the ACC/AHA offers a class I recommendation for prophylactic ICD placement for the primary prevention of SCD in patients with ischemic cardiomyopathy and reduced EF, identification of those most likely to require the device remains challenging. Our current strategy continues to rely primarily on estimation of LVEF as obtained from angiography, echocardiography, nuclear imaging or cardiac MRI. Of patients who received a primary prevention ICD, appropriate ICD therapies occur in only 25 % of patients after 5 years [4]. Moreover, device therapies for ventricular tachycardia (VT) overestimate the incidence of aborted sudden cardiac arrest, with conventional programming strategies (e.g., short durations between detection and treatment, use of anti-tachycardia pacing, and treatment of a wide range of VT rates). Many therapies have subsequently been found to treat self-terminating ventricular arrhythmias that do not lead to SCD [5]. Thus, while prophylactic ICD therapy saves lives, there continues to be a need to develop better risk stratification approaches that can identify those within the primary prevention ICD population (i.e., with an EF ≤35 %) at highest risk of arrhythmic death. An equally important unmet need reflects the sobering fact that we currently have no way to prospectively identify those at risk of arrhythmic death with ejection fractions greater than 35 %. While the annual rate of SCD in this population is lower, they constitute the vast majority of patients that will ultimately succumb to arrhythmic death [6].

Radiotracer-Based Imaging of the Cardiac Sympathetic Nervous System—Factors Determining Alterations in Myocardial Tracer Activity

Advances in cardiac molecular imaging have paved the way for the emergence of radiotracers capable of characterizing myocardial sympathetic innervation in vivo. The utility and accurate interpretation of these radiotracers are based on the understanding of the biologic fate of the neurotransmitter, norepinephrine. Sympathetic projections from the central nervous system synapse primarily in the stellate ganglia, and post-ganglionic fibers travel in parallel with the epicardial coronary arteries to innervate the epicardium and subsequently, homogeneously distribute to the inner layers of the heart. Sympathetic activation results in the release of norepinephrine into the synaptic cleft to bind to β-adrenoreceptors located on the cardiomyocyte membrane. Sympathetic activity is terminated by the reuptake of norepinephrine from the synaptic cleft to the neuronal varicosities via norepinephrine transporter (NET) or 'Uptake-1' and undergoes degradation or repackaging. Although several other targets for sympathetic nerve imaging have been investigated, the bulk of the clinical data on radiotracer-based imaging is based on the evaluation of NET reuptake activity using norepinephrine analogs (Fig. 1). For conventional nuclear imaging, ^{123}I-meta-iodobenzylguanidine (^{123}I-MIBG) is the principal tracer. Using PET imaging, the most common norepinephrine analog used is ^{11}C-meta-hydroxyephedrine (^{11}C-HED). The myocardial retention of ^{11}C-HED and ^{123}I-MIBG are both dependent on the NET reuptake mechanism, as evidenced by reduced retention with NET blockade. Both radioligands compete with norepinephrine released from presynaptic sympathetic nerves as well as circulating norepinephrine levels in blood. Because of this, myocardial radioligand uptake is functionally reduced when there is elevated global myocardial sympathetic tone as well as elevated circulating norepinephrine levels as in heart failure. Retention of ^{123}I-MIBG and ^{11}C-HED in the myocardium can also be reduced by inhibiting the NET pharmacologically (e.g. using alpha-2 agonists), chemical sympathectomy using the topical application of phenol on the cardiac surface, or surgical denervation immediately following cardiac transplantation. Cardiac re-innervation after global denervation occurs slowly and remains relatively minor many years after cardiac transplantation [7].

While both MIBG and HED can assess myocardial sympathetic nerve function, there are differences that are important to consider. First, the target to background ratio can diminish due to increased competition from myocardial norepinephrine release as heart failure severity advances making it difficult to characterize regional ^{123}I-MIBG uptake with conventional SPECT. Thus, most clinical studies employing ^{123}I-MIBG are based on planar imaging of global myocardial uptake or washout compared with activity in a reference mediastinal region of interest. While the target to background activity of ^{11}C-HED is more favorable and allows attenuation corrected images as well as kinetic analyses to be performed, it requires an on-site cyclotron for synthesis and is not available for widespread clinical distribution. Finally, animal studies suggest that nonneuronal uptake can vary between tracers [8, 9]. When compared with ^{123}I-MIBG, ^{11}C-HED appears to have significantly less extraneuronal uptake and it is resistant to degradation by monoamine oxidase and catecholamine-*O*-methyltransferase. These differences may favor the detection of regional variations in myocardial sympathetic innervation using ^{11}C-HED.

Regional Myocardial Sympathetic Denervation from Reversible and Irreversible Ischemia

Early work in canine models demonstrated that sympathetic denervation occurred following transmural myocardial infarction. Denervation occurs in irreversibly injured myocardium, the entire myocardial region at risk of ischemia, and normal myocardium that is apical from an infarcted region [10]. Similar changes have been demonstrated in humans with myocardial infarction where the volume of denervated myocardium exceeds infarcted myocardium [11–15]. Viable but denervated myocardium, exhibits a 'hypersensitivity response' to norepinephrine and isoproterenol infusion with accentuated shortening of the effective refractory period [16]. In addition, norepinephrine infusion enhances induction of ventricular arrhythmias during programmed ventricular stimulation. This has led to the hypothesis that inhomogeneity in sympathetic innervation and/or denervation supersensitivity creates a substrate favorable to arrhythmogenesis by increasing spatial dispersion of action potential duration during sympathetic activation.

In addition to myocardial infarction, inhomogeneity in myocardial sympathetic innervation has also been demonstrated in chronic coronary artery disease and animal models of chronic reversible ischemia that results in hibernating myocardium [8, 9, 12, 13, 17–24]. These changes are accompanied by an increased risk of SCD from VT/VF in the absence of severely depressed global function as well as acute or chronic infarction [25–27]. Myocardial uptake of ^{123}I-MIBG was reduced in swine with hibernating myocardium with the greatest reduction seen in the subendocardium [8], coinciding with the region with the most severe limitation in coronary flow reserve. PET imaging using ^{11}C-HED demonstrated even larger reductions in ^{11}C-HED uptake [9]. These imaging findings were supported by ex vivo western analyses of sympathetic markers and physiologic studies [28]. Thus, both reversible (acute and chronic ischemia) and irreversible ischemia (infarction) can lead to regional inhomogeneity in myocardial sympathetic innervation. These changes reflect the fact that myocardial sympathetic nerves are exquisitely sensitive to ischemia [29].

Sympathetic re-innervation and nerve sprouting may also contribute to inhomogeneity in myocardial sympathetic innervation and lethal ventricular arrhythmias [30]. Following infarction, there is increased cardiac expression of nerve growth factor which is critical for sympathetic nerve survival. Likewise, growth-associated protein-43 (GAP43), a marker of neuronal growth and nerve sprouting, increases at the border zone between normal and infarcted tissue [31]. Similar changes are seen in chronic reversible ischemia associated with hibernating myocardium [32]. These areas of neural remodeling and hyperinnervation may further contribute to inhomogeneity leading to lethal ventricular arrhythmias and SCD.

Clinical Evidence of Impaired Myocardial Sympathetic Innervation in Left Ventricular Dysfunction

Myocardial sympathetic denervation is prevalent among patients with ischemic heart disease. In a small study of patients with known coronary artery disease (CAD), 91 % of the patients had some degree of reduced myocardial uptake on ^{123}I-MIBG SPECT, and this

could occur in the absence of a prior history of a myocardial infarction (MI) [21]. The magnitude of reduced ^{123}I-MIBG uptake was found to be related to stenosis severity. Patients with a prior myocardial infarction had greater reductions in ^{123}I-MIBG uptake than those without infarction (16 vs. 7 % of LV mass). The benefit of cardiac neurohormonal modulation was demonstrated by large randomized trials studying the use of beta-blockers in heart failure [33–35]. Survival benefit was attributed to preventing heart failure progression as well as reducing sudden cardiac death and was hypothesized to be due to the suppression of myocardial sympathetic activity. This was confirmed by subsequent in vivo radionuclide studies evaluating the effects of beta-blockers on global ^{123}I-MIBG uptake. Milliano et al. evaluated the effect of metoprolol therapy on cardiac sympathetic innervation in 59 patients with heart failure [36]. As compared with baseline imaging, myocardial ^{123}I-MIBG uptake increased by approximately 22 % in patients receiving metoprolol for 6 months while it decreased by 7.8 % in placebo controls. The increase in ^{123}I-MIBG uptake with metoprolol-paralleled reverse left ventricular (LV) remodeling with a reduction in LV end-diastolic diameter and an increase in the LVEF. Regional improvement in cardiac sympathetic innervation was reported in a randomized trial of carvedilol [37]. In this study, defect size on ^{123}I-MIBG SPECT decreased among patients on carvedilol (20 to 15 %, p=0.03) with no change in placebo controls (22 vs. 21 %, p=NS). Thus, these imaging studies indicate that the myocardial uptake of norepinephrine analogs is favorably increased in response to blocking neurohormonal activation with beta-blockers in patients with heart failure. This most likely is an indirect action and secondary to reduced myocardial sympathetic nerve activity resulting from improvements in left ventricular function and functional class. Nevertheless, the studies indicate that the pharmacological treatment of heart failure can modulate the uptake of norepinephrine analogs.

Myocardial Sympathetic Denervation Predicts Clinical Outcomes

A logical extension of these data is determining whether sympathetic nerve imaging can predict cardiovascular events and impact prognosis. Merlet et al. followed 90 patients with cardiomyopathy (mixed ischemic and non-ischemic etiology) for up to 27 months and found that the heart to mediastinum ratio (HMR) of ^{123}I-MIBG uptake was the most potent predictor of survival [38]. These findings were subsequently expanded to show that the ^{123}I-MIBG HMR was the most important clinical predictor of cardiac mortality after 54 months of follow-up [39]. This predictive capacity was independent of the etiology of left ventricular dysfunction and was even prognostic among those with only mildly reduced EF (40–50 %) [39].

The largest prospective study evaluating global ^{123}I-MIBG uptake and clinical outcomes was the AdreView Myocardial Imaging for Risk Evaluation in Heart Failure study (ADMIRE-HF). In this study, planar ^{123}I-MIBG and SPECT perfusion imaging were performed in 961 patients with NYHA class II or III heart failure (HF) and LVEF ≤35 % [40]. The majority of patients (66 %) had ischemic cardiomyopathy. Over a median follow-up of 17 months, the primary composite end-point (heart failure progression, arrhythmic events and cardiac death) occurred more frequently among those with a global reduction in sympathetic innervation (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 were non-sustained VT. SCD, resuscitated sudden cardiac arrest, and appropriate ICD discharges (shock or anti-tachycardia pacing) were a small portion of the total composite end-points (21 %) [40]. Quantification of regional defects was attempted in a subgroup of patients but did not provide any additional value to global indices of ^{123}I-MIBG uptake in predicting prognosis [40].

A sub-analysis of the ADMIRE-HF study explored whether ^{123}I-MIBG HMR provided any improvement in risk stratification over LVEF. The ADMIRE-HF LVEF values reported by the core laboratory (some core LVEF measurements were >35 %) were stratified by a late HMR of 1.6, and the combined ADMIRE-HF end-points were estimated in each group [41]. A late HMR of <1.6 conferred, a greater risk of death and arrhythmic events across all LVEF subgroups. Interestingly, among subjects with an LVEF >40 %, a late HMR >1.6 was not associated with any risk of death or an arrhythmic event over the follow-up period. In contrast, individuals with an LVEF >40 % and a late HMR <1.6 had a 7.5 %/100 person-years risk of death and arrhythmic events. While this was a post-hoc analysis, the observations raise the possibility that assessing global cardiac sympathetic innervation may ultimately aid in identifying individuals at an increased risk of arrhythmic death who would otherwise be categorized as low risk based upon relatively preserved LV function.

In order to determine the most prognostic end-point associated with altered global ^{123}I-MIBG uptake, Verschure et al. recently performed a patient level meta-analysis of 636 heart failure patients [42••]. Over a mean follow-up of 37 months, HMR was able to predict all categories of cardiac events, with the strongest predictive value for composite cardiac events, all-cause mortality, and cardiac mortality. Interestingly, the weakest univariate predictor of ^{123}I-MIBG HMR was for arrhythmic events. In multivariate analysis, only NYHA heart failure class and age were independently associated with arrhythmias.

In contrast to these results, Tamaki et al. showed that an alternate assessment of ^{123}I-MIBG can predict SCD [43]. Among 106 patients with an EF <40 % followed up for an average of 65 months, three measures of ^{123}I-MIBG (early HMR (at 20 min), delayed HMR (at 200 min) and *m*IBG washout ratio (WR; between 20 and 200 min after injection)] predicted SCD. However, by multivariate analysis, only WR and EF remained independent predictors. In a separate multivariate analyses, WR was the only ^{123}I-MIBG parameter that was an independent predictor of pump failure death and total cardiac mortality. 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. Thus, the generalizability of these results to the contemporary management of patients on optimal medical therapy for heart failure at the time of imaging is uncertain.

Incremental Prognostic Value of Regional Sympathetic Denervation in Ischemic Cardiomyopathy

Bax et al. provided one of the first clinical studies exploring the relation between regional sympathetic denervation and arrhythmic events in a phase 2 study of cardiac ^{123}I-MIBG imaging [44]. Fifty patients with ischemic cardiomyopathy and an LVEF ≤40 % referred for electrophysiological (EP) study for unexplained syncope or non-sustained VT underwent

planar and SPECT ^{123}I-MIBG imaging. Early and late HMR were determined from the planar images, while early and late ^{123}I-MIBG summed scores (reflecting regional defect size) were obtained from the SPECT data. Thirty patients had a positive EP study and demonstrated significantly greater late ^{123}I-MIBG SPECT summed score compared with patients with a negative EP study. There were no differences in the planar early or late HMR between those with and without a positive EP study. All patients had ischemic cardiomyopathy, but infarct sizes (Technetium-99 m SPECT) were not different between the two groups. The only independent predictor of a positive EP study (sustained VT) was the late ^{123}I-MIBG SPECT summed score. This supports the potential of regional sympathetic denervation to predict arrhythmic events. Similar to reports from animal studies [45], the burden of sympathetic denervation on SPECT was much larger than the SPECT perfusion defect. Nevertheless, the size of the denervation-perfusion mismatch did not predict a positive EP study. A recently published reanalysis of the images from these patients focused on assessing ^{123}I-MIBG uptake in the scar and border zone (40–60 % of normal perfusion) [46]. With this approach, ^{123}I-MIBG uptake in the border zone was shown to predict inducibility of sustained VT at EP study.

These studies were subsequently expanded to determine whether the association of regional denervation and inducible ventricular arrhythmia among patients with ischemic and non-ischemic cardiomyopathy correlated with ICD therapies. One hundred and sixteen patients on optimal medical therapy after receiving any clinically indicated re-vascularization therapy underwent planar and SPECT ^{123}I-MIBG imaging and SPECT Tc 99 m perfusion imaging [47]. Over an average follow-up period of 23 months, appropriate ICD therapy (shock or anti-tachycardia pacing) occurred in 21 % patients. ICD implantation for secondary prevention (vs. primary prevention) and late ^{123}I-MIBG SPECT defect size were the only independent predictors of ICD therapy and cardiac death. The authors found that ICD therapies were more prevalent (40 vs. 3 %) among those with large ^{123}I-MIBG defects (summed score >26) when compared with those with smaller defects. There was no relationship between the presence or size of denervation-perfusion mismatch and ventricular arrhythmias.

Recently, PET imaging with ^{11}C-HED has been employed to quantify the extent of sympathetic denervation with cause specific mortality for sudden cardiac arrest [48]. The Prediction of Arrhythmic Events with Positron Emission Tomography (PAREPET) study specifically evaluated the occurrence of sudden cardiac arrest (SCA) among patients with ischemic cardiomyopathy (EF≤35 %) in relation to the volume of denervated myocardium using PET [49••]. The study enrolled 204 patients, who underwent PET assessment (Fig. 2) of myocardial perfusion ($^{13}NH_3$—ammonia retention), myocardial denervation (^{11}C-meta-hydroxyephedrine (^{11}C-HED)) and viability (^{18}F-2-deoxyglucose (^{18}FDG)). Thirty-three patients experienced SCA which included arrhythmic death (SCD) or ICD discharge for aborted arrhythmic death (ventricular fibrillation or VT >240 beats/min). Other device therapies including treatments for VT at rates <240 were not considered SCA surrogates. Patients developing SCA had a significantly greater volume of denervated myocardium and viable-denervated myocardium when compared with those without SCA, and 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 and patients in the highest tertile of denervation had an SCA rate of 6.7 % per year (Fig. 3). In a multivariate analysis, the magnitude of denervated myocardium was the only independent predictor of SCA from PET imaging. Global ^{11}C-HED retention fraction (analogous to the ^{123}I-MIBG HMR) was not different among those with and without SCA. This study was the first to suggest a relationship between viable-denervated myocardium and lethal arrhythmic events. This parallels the preclinical observations in swine with hibernating myocardium [9, 26, 27]. Nevertheless, only the total volume of denervated myocardium remained a significant predictor in the multivariate analysis [44, 47]. Interestingly, scar volume assessed using ^{18}FDG was not a multivariate predictor of arrhythmic death.

Clinical Implications and Future Perspectives

The available data have consistently shown that imaging of cardiac sympathetic innervation provides independent prognostic information in patients with reduced LV systolic function. Recent meta-analyses have suggested that the strongest predictive potential of ^{123}I-MIBG HMR is for all-cause cardiac mortality, as well as a composite including non-lethal clinical events [42••, 50••]. Our current medical approach to heart failure management recommends up-titration of medications as clinically tolerated and the clinical utility of incorporating ^{123}I-MIBG imaging into managing heart failure patients remains unclear.

The potential clinical utility of imaging sympathetic innervation is much more obvious with regard to the end-point of preventing lethal arrhythmias and targeting ICDs for the primary prevention of sudden death. Unfortunately, the majority of studies have lumped all arrhythmic events and included those of dubious clinical impact as ‘appropriate ICD therapies.’ These not only over estimate SCA by nearly threefold [51, 52] but approaches to reduce ICD therapies for these nonmalignant ventricular arrhythmias actually improve survival [5]. Thus, although ‘appropriate ICD therapies’ is a convenient end-point, future studies would benefit from employing a more restrictive end-point that more closely approximates the observed benefit of ICD therapy as recently employed in the PAREPET trial [49••].

The available data also suggests that regional, rather than global, assessment of sympathetic innervation will be more accurate for predicting arrhythmic death and targeting ICD therapy. Although this assessment is possible with ^{123}I-MIBG and conventional SPECT imaging (and potential improvements are likely with new imaging technologies), there will continue to be inherent limitations due to radionuclide imaging characteristics and photon attenuation. PET approaches therefore appear to hold more promise. Nevertheless, the preeminent PET sympathetic nerve tracer, HED, requires a local cyclotron and radiochemistry support. Thus, widespread clinical application will require a tracer incorporating a longer half-life isotope (e.g., ^{18}F labeled LMI1195, Lantheus Medical Imaging) [53, 54], which could be regionally produced and then transported to individual PET centers for clinical use (as is currently used for oncologic imaging with ^{18}F-2-deoxyglucose (FDG)).

Clinical assessment of the risk for SCA has two obvious clinical applications. The first would be to recommend additional therapy for those at elevated risk of SCA. At this point,

the only specific therapy that could be realistically considered would be an ICD. Furthermore, expanding the clinical indication for ICDs would be challenging due to (a) the high cost of these devices and (b) the widespread recognition that ICDs are not efficiently used in those with current primary prevention indications (as previously noted, appropriate ICD therapies occur in only 25 % of patients after 5 years [4]). Alternatively, sympathetic imaging could be used to identify patients at low risk of SCA among those who are currently considered for a primary prevention ICD. For example, the PAREPET study enrolled subjects who were already eligible for an ICD. As illustrated in Fig. 4, the absence of all four independent risk factors was associated with a very low risk of SCA (<1 %/ year). This is a lower rate of SCA than in patients with coronary artery disease and mild LV dysfunction [55–57] who are not considered candidates for ICD therapy. Furthermore, this subgroup comprised over 44 % of the PAREPETcohort. Thus, with independent validation of these results and additional studies to determine the optimal time interval for retesting, it may become possible to safely delay implanting an ICD for low-risk patients who have a current clinical indication based solely on ejection fraction. A recent meta-analysis has also suggested that the addition of ^{123}I-MIBG HMR was particularly helpful for the downward reclassification of a low-risk cohort [58••].

Conclusion

In conclusion, imaging cardiac sympathetic innervation provides prognostic information in patients with left ventricular dysfunction, and numerous studies have documented that this information is independent of routine clinical and demographic parameters. Nevertheless, the clinical translation of these findings to routine patient care remains unclear. Although there are clearly unanswered questions regarding optimal tracers and assessment methods, there appears to be sufficient preliminary data to move in the direction of pragmatic clinical trials which incorporate cardiac sympathetic imaging into algorithms with therapeutic implications. The design and funding of these studies will present considerable challenges to interested investigators, but they are critical if cardiac sympathetic imaging is going to enter the clinical armamentarium.

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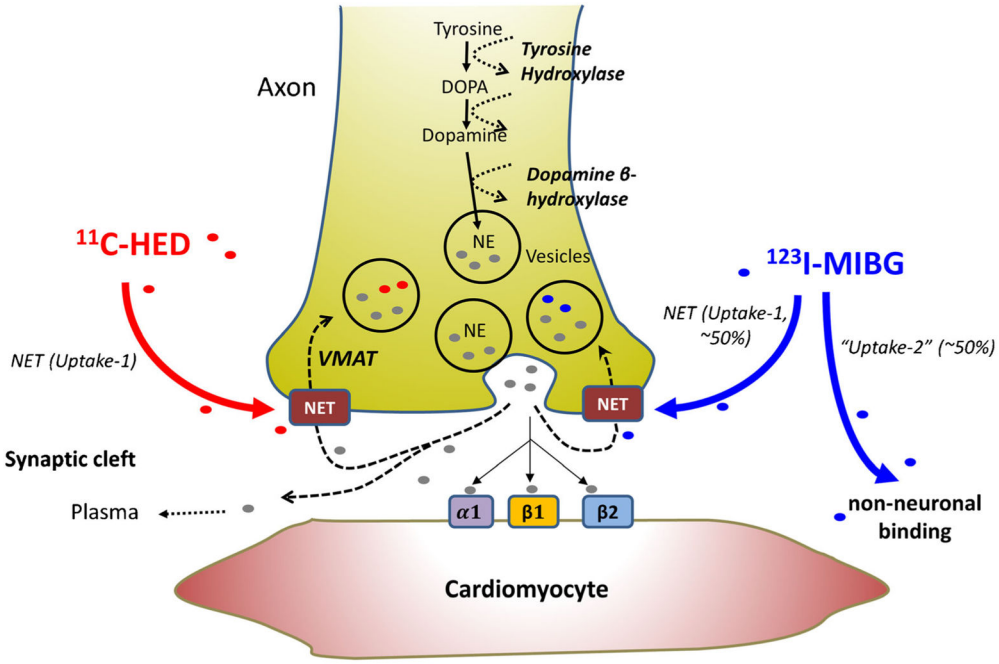

Fig. 1.

Cardiac sympathetic nerve transmission and tracer uptake. Schematics of sympathetic transmission and neuronal uptake of ^{11}C-HED and ^{123}I-MIBG for imaging of sympathetic neuronal innervation. Norepinephrine (*NE*) is synthesized and packaged in the nerve terminals and released into the synaptic cleft. Released NE binds to target receptors or is recycled to the sympathetic nerve terminal via norepinephrine transporter (*NET*) for repackaging or degradation. ^{11}C-HED and ^{123}I-MIBG radiotracers are also incorporated into the nerve terminals using NET-dependent mechanism. *VMAT* vesicular monoamine transporter, *DOPA* 3,4-dihydroxyphenylalanine

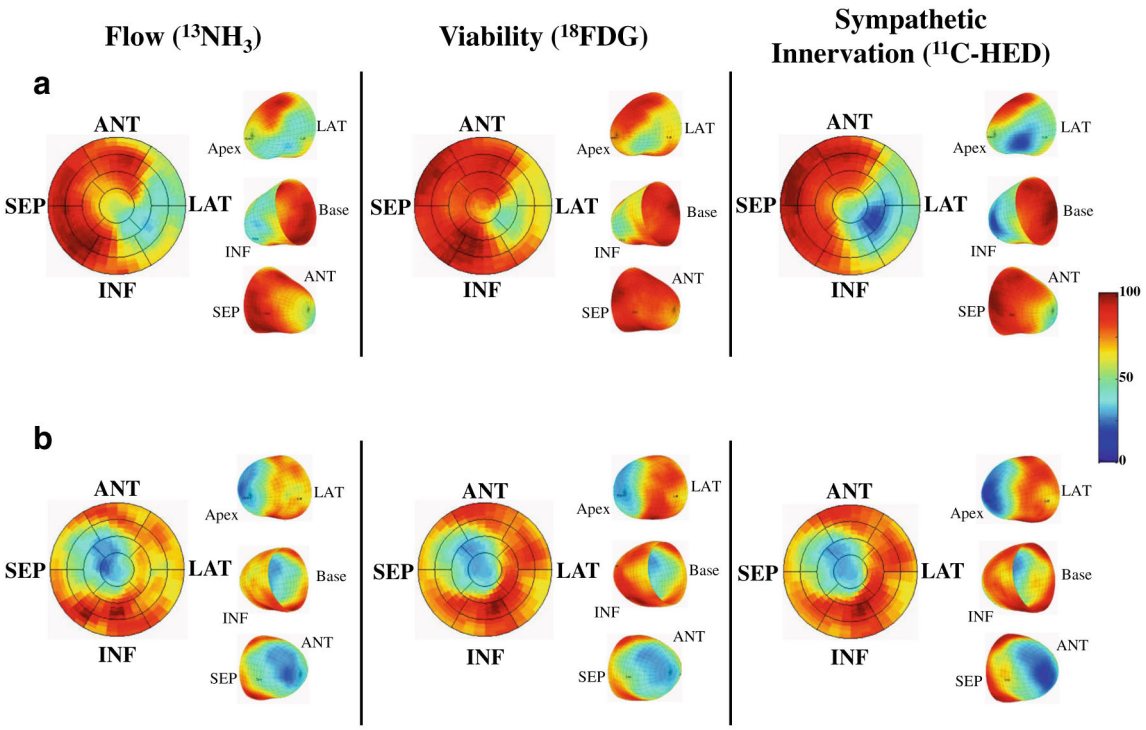

Fig. 2.

PAREPET imaging of myocardial flow, viability, and sympathetic innervation. **a** A subject who experienced SCA. There is a mismatch in infarct size (reduced ^{18}F-2 deoxyglucose, ^{18}FDG which was administered during a euglycemic-hyperinsulinemic clamp) 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}FDG), there was reduced perfusion (^{13}N-ammonia ($^{13}NH_3$)) with preserved ^{18}FDG indicating hibernating myocardium. In contrast, a subject with matched reductions in flow, infarct volume, and sympathetic denervation is shown in (**b**). (*ANT* anterior, *INF* inferior, *LAT* lateral, *SEP* septum). (Reprinted with permission from Elsevier [49••])

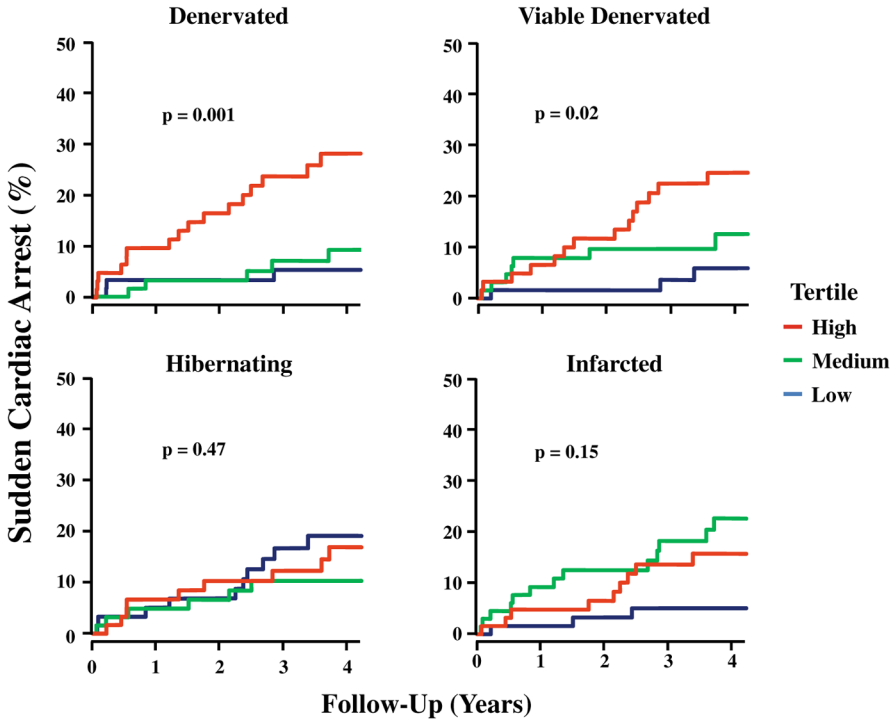

Fig. 3.

PAREPET imaging parameters and SCA. Kaplan-Meier curves show the incidence of SCA for tertiles of PET-defined myocardial substrates (median follow-up, 4.1 years). As continuous variables, the total volume of denervated myocardium as well as viable-denervated myocardium predicted SCA. Neither infarct volume nor hibernating myocardium was significant as continuous variables. (Reprinted with permission from Elsevier [49••])

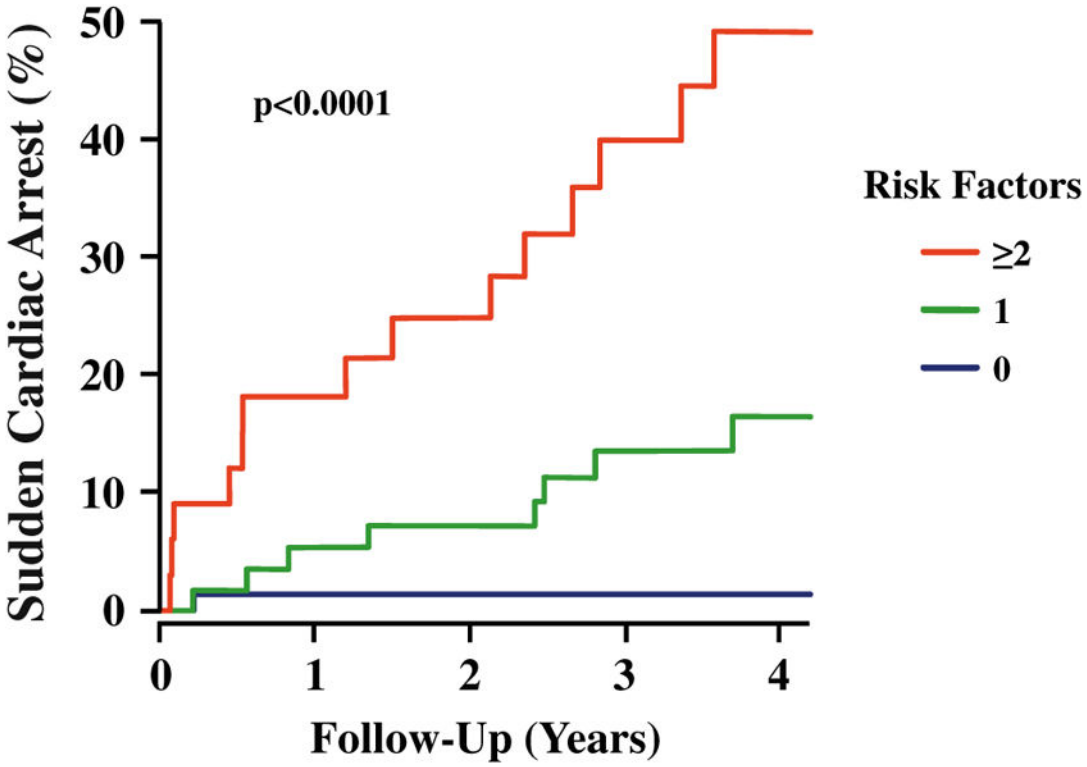

Fig. 4.

SCA risk factor model from PAREPET. Kaplan-Meier curves illustrating highly significant differences in the incidence of SCA in relation to the number of risk factors present (p<0.0001). Subjects with no risk factor (*blue*, 44 % of cohort) had an annual rate of SCA <1 %. With two or more risk factors (*red*, 20 % of cohort), the annual risk of SCA increased to ~12 %. Patients with one risk factor (*green*, 36 % of cohort) had an intermediate risk of SCA (~4 %/year). (Reprinted with permission from Elsevier [49••])