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Regional Myocardial Sympathetic Denervation Predicts the Risk of Sudden Cardiac Arrest in Ischemic Cardiomyopathy

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Abstract

Objectives—The PAREPET (Prediction of ARrhythmic Events with Positron Emission Tomography) study sought to test the hypothesis that quantifying inhomogeneity in myocardial sympathetic innervation could identify patients at highest risk for sudden cardiac arrest (SCA).

Background—Left ventricular ejection fraction (LVEF) is the only parameter identifying patients at risk of SCA who benefit from an implantable cardiac defibrillator (ICD).

Methods—We prospectively enrolled 204 subjects with ischemic cardiomyopathy (LVEF ≤35%) eligible for primary prevention ICDs. Positron emission tomography (PET) was used to quantify myocardial sympathetic denervation (^{11}C-meta-hydroxyephedrine [^{11}C-HED]), perfusion (^{13}N-ammonia) and viability (insulin-stimulated ^{18}F-2-deoxyglucose). The primary endpoint was SCA defined as arrhythmic death or ICD discharge for ventricular fibrillation or ventricular tachycardia >240 beats/min.

Results—After 4.1 years follow-up, cause-specific SCA was 16.2%. Infarct volume (22 ± 7% vs. 19 ± 9% of left ventricle [LV]) and LVEF (24 ± 8% vs. 28 ± 9%) were not predictors of SCA. In contrast, patients developing SCA had greater amounts of sympathetic denervation (33 ± 10% vs. 26 ± 11% of LV; p = 0.001) reflecting viable, denervated myocardium. The lower tertiles of sympathetic denervation had SCA rates of 1.2%/year and 2.2%/year, whereas the highest tertile had a rate of 6.7%/year. Multivariate predictors of SCA were PET sympathetic denervation, left

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APPENDIX

For a supplemental methods section, please see the online version of this article.

ventricular end-diastolic volume index, creatinine, and no angiotensin inhibition. With optimized cut-points, the absence of all 4 risk factors identified low risk (44% of cohort; SCA <1%/year); whereas ≥2 factors identified high risk (20% of cohort; SCA ~12%/year).

Conclusions—In ischemic cardiomyopathy, sympathetic denervation assessed using ^{11}C-HED PET predicts cause-specific mortality from SCA independently of LVEF and infarct volume. This may provide an improved approach for the identification of patients most likely to benefit from an ICD. (Prediction of ARrhythmic Events With Positron Emission Tomography [PAREPET]; NCT01400334)

Keywords

^{11}C-meta-hydroxyephedrine; myocardial viability; positron emission tomography; sudden cardiac arrest; sympathetic denervation

Numerous clinical and demographic variables have been associated with an increased risk of arrhythmic death, and many electrophysiological approaches have been proposed and evaluated in an attempt to better identify the patient population at highest risk of future arrhythmic death (1,2). However, despite multiple large clinical trials performed during the last 30 years, left ventricular ejection fraction (LVEF) remains the only parameter clinically used to distinguish high- and low-risk groups. Based on this approach, randomized trials have unequivocally established the benefit of prophylactic implantable cardiac defibrillator (ICD) placement to prevent arrhythmic death and improve survival in patients with a LVEF ≤35% (3–5). Nevertheless, the majority of patients never require device therapy to prevent a lethal ventricular arrhythmia. The ability to identify risk of arrhythmic death independently of LVEF could better target therapy among current ICD candidates, as well as identify patients with LVEF >35% who are at high risk of SCA (1,2). Although the latter population has a lower rate of arrhythmic death, it actually accounts for a larger number of arrhythmic events (6).

Previous basic and clinical studies have demonstrated an important role for sympathetic activation in the development of lethal ventricular arrhythmias, and inhomogeneity in myocardial sympathetic innervation may create a myocardial substrate particularly vulnerable to arrhythmic death (7). This inhomogeneity can reflect sympathetic denervation from infarction, as well as reversible ischemia. For example, in reperfused infarcts, the extent of sympathetic denervation exceeds infarct volume and approximates the entire area at risk of myocardial ischemia (8). In chronic coronary disease, reversible ischemia (from angina or silent ischemia) also creates inhomogeneity in myocardial sympathetic innervation that is independent of infarction, occurring in both stunned and hibernating myocardium (9). Pre-clinical models of hibernating myocardium have a high rate of arrhythmic death from spontaneous ventricular tachycardia (VT)/ventricular fibrillation (VF) that develops in the absence of infarction and heart failure (10), and ^{11}C-meta-hydroxyephedrine (^{11}C-HED) positron emission tomography (PET) demonstrates extensive sympathetic denervation (11).

On the basis of these observations, we tested the hypothesis that quantifying inhomogeneity in myocardial sympathetic innervation and/or hibernating myocardium increased the risk of arrhythmic death independently of LV function. The PAREPET (Prediction of ARrhythmic Events with Positron Emission Tomography) study was designed as an initial step toward this goal evaluating primary prevention ICD candidates with coronary artery disease (12).

Methods

The PAREPET trial, sponsored by the National Institutes of Health, is a prospective, observational cohort study designed to determine whether imaging hibernating and/or

denervated myocardium can predict arrhythmic death in ischemic cardiomyopathy. This study was approved by the University at Buffalo and Veterans Affairs Western New York Healthcare System Institutional Review Boards. Methodological details of the study have been published and are provided in the Online Appendix (12).

Study design

The study population (n = 204) included patients with ischemic cardiomyopathy who were eligible to receive a primary prevention ICD (pre-enrollment LVEF ≤35% for Class ≥II and ≤30% for Class I). They had stable ischemic heart disease and heart failure on optimal medical therapy, and were not considered candidates for coronary revascularization. Exclusion criteria included a prior cardiac arrest or ICD discharge, recent infarction (<30 days), or revascularization (PCI <3 months; bypass grafting <1 year) (12).

Echocardiography and PET

Two-dimensional echocardiography (Sonos 7500, Philips Medical Inc., Andover, Massachusetts) was performed on the day of PET imaging as previously described (12,13). An echocardiographer blinded to events quantified cardiac volumes, LVEF, and mitral regurgitation, as recommended by the American Society of Echocardiography.

The PET imaging was performed on a ECAT EXACT HR+ (CTI, Knoxville, Tennessee) PET scanner (15.5 cm axial field-of-view; resolution ~5.4 mm^3 full-width-at-half-maximum) (12,13). Sympathetic innervation was assessed with ^{11}C-HED [740 MBq], resting perfusion with $^{13}NH_3$ [740 MBq], and viability with ^{18}F-2-deoxyglucose (^{18}FDG) [241MBq] during a hyperinsulinemic-euglycemic clamp (13). Attenuation correction was performed using a ^{68}Ge rod source (12,13). Of the planned 585 PET images, 96% were completed and quantifiable with 176 subjects having complete data. Results from imaging were not provided for patient management. Radiation exposure was <12 mSv.

Quantitative PET analysis

Blinded analysis used Flow-Quant (Ottawa Heart Institute, Ottawa, Ontario, Canada) (13,14) and decay corrected reconstructed images (zoom 2; Hann filter cutoff 0.3 cycles/pixel). Late uptake defined the left ventricle (LV) with bottle-brush sampling (15). Late myocardial uptake was averaged from 4 frames of data for each imaging set: 15 to 60 min after ^{11}C-HED; 3 to 19 min after $^{13}NH_3$; 15 to 40 min after ^{18}FDG. We normalized myocardial activity to the highest 5% of sectors (496 sector model) (15). Normal $^{13}NH_3$ and ^{18}FDG uptake were ≥80% of peak (12,14). Normal ^{11}C-HED uptake was considered ≥75% of peak, on the basis of the estimated ratio of reduced versus normal ^{11}C-HED retention fraction among zones with normal resting flow (16). All PET parameters were expressed as % of LV. Infarcted and hibernating myocardium were quantified from a mismatch analysis between $^{13}NH_3$ and ^{18}FDG (14). To evaluate the potential influence of global downregulation in ^{11}C-HED uptake, ^{11}C-HED retention was determined for the segment with maximal ^{11}C-HED uptake in each subject. ^{11}C-HED retention (min^{-1}) was calculated by dividing mean segment activity from the late uptake image by the integrated arterial activity (from 0 to 60 min) (11).

Classification of events

Subjects were contacted at 3-month intervals to review interval ICD therapy, hospitalizations, and symptoms. The primary endpoint was sudden cardiac arrest (SCA). This included arrhythmic death or ICD discharge for VF or VT >240 beats/min (12). The frequency of ICD discharge for these arrhythmias approximates the reduction in mortality

with an ICD (12,17,18). Clinical notes and electrograms from ICD discharges were independently reviewed.

We classified deaths (i.e., SCA, cardiac nonsudden and noncardiac) using modified Hinkle-Thaler criteria (19,20). Available details (i.e., medical records, witnesses, family, death certificates), activity levels, and symptoms before death were reviewed by 2 cardiologists. In the event of disagreement, a consensus was reached with a third reviewer. Cardiac transplantation and arrhythmic events with end-stage heart failure or hospice care were classified as cardiac nonsudden deaths (19). Revascularization procedures were performed on 26 subjects after enrollment.

Statistical analyses

Data are presented as mean ± SD. Subjects with and without SCA were compared with unpaired Student *t* tests (continuous data) and chi-square test analysis (categorical data). The time to SCA was analyzed graphically using Kaplan-Meier plots and was tested using Cox proportional hazard models and the log-rank statistic. Optimal cut-points for continuous variables were determined retrospectively by values that maximized the log-rank statistic. Stepwise selection was used to generate the optimal multivariate model to predict time to SCA from PET, demographics, medications, echocardiographic, hemodynamic, and laboratory parameters. All statistical analyses were performed with commercial software (Microsoft Excel version 2010, [Microsoft, Redmond, Washington] and SAS version 9.1, [SAS Institute Inc., Cary, North Carolina]).

Results

Table 1 summarizes demographic variables. Average LVEF was 27 ± 9%, age was 67 ± 11 years, New York Heart Association functional class was 2.1 ± 0.8, and Canadian Cardiovascular Society angina class was 1.8 ± 0.7. There were 21 women (10%). Diabetes was present in 47%, 78% had prior coronary revascularization, and 81% had an ICD prior to an event. Medical therapy was very good, with almost all subjects treated with anti-platelet therapy or warfarin (99%), β-blockers (96%), and angiotensin inhibition therapy (angiotensin-converting-enyzme inhibitor or angiotensin receptor antagonist, 90%).

PET quantification of denervated, infarcted, and viable myocardium

PET images from 2 representative subjects comparing resting flow ($^{13}NH_3$), viability (insulin-stimulated ^{18}FDG), and myocardial sympathetic innervation (^{11}C-HED) are shown in Figure 1. Quantitative image analysis determined that the average infarct volume was 20 ± 9% of the LV. In comparison, the average volume of denervated myocardium was considerably larger, averaging 27 ± 11% of the LV ($p < 0.001$ vs. infarcted), with 8 ± 6% of the LV denervated, but viable. Hibernating myocardium (viable myocardium with reduced resting perfusion) was uncommon, reflecting the high prevalence of prior revascularization, and averaged 3 ± 3% of the LV.

Clinical and imaging correlates of SCA

During a median follow-up of 4.1 years (range: 2.5 to 7.2 years), there were 33 adjudicated sudden cardiac arrests. There were no differences between the 22 subjects with arrhythmic death versus the 11 with ICD discharges for VF or VT >240 beats/min. All SCA events occurred in men ($p = 0.06$). Selected imaging parameters associated with SCA are summarized in Table 2. Subjects developing SCA had significantly larger volumes of denervated and viable denervated myocardium, whereas infarct volume and hibernating myocardium were not different. Although the LVEF and LV mass were not significantly different, those who experienced SCA had larger LV volume indices and more mitral

regurgitation. Among laboratory parameters, serum creatinine and B-type natriuretic peptide (BNP) were higher in patients developing SCA (Table 1).

Quantitative imaging and SCA

The primary analysis of the PAREPET study was the evaluation of PET imaging parameters as continuous variables to predict time to SCA. The cumulative event rate curves of tertiles for each PET parameter are summarized in Figure 2. The volume of denervated myocardium had the strongest correlation with SCA ($p = 0.001$) (Table 3). Patients in the highest tertile of sympathetic denervation had an SCA event rate of ~6.7%/year, whereas the intermediate and lowest tertiles had event rates of 2.2%/year and 1.2%/year, respectively. Each 1% increase in the volume of denervated myocardium was associated with a 5.7% increase in the risk of SCA. Similarly, the volume of viable denervated myocardium was significantly associated with the time to SCA ($p = 0.025$), with risk of SCA increasing by 6.7% for every 1% increase in viable, denervated myocardium. The ability of denervated myocardium to predict SCA was not influenced by any global downregulation in ^{11}C-HED uptake. The ^{11}C-HED retention in segments with maximal ^{11}C-HED uptake was 0.136 ± 0.036 min^{-1}, with no difference among those with and without subsequent SCA (0.134 ± 0.027 min^{-1} vs. 0.137 ± 0.037 min^{-1}; $p=0.69$).There was no significant association between SCA and the volume of infarcted or hibernating myocardium (Table 3).

Other parameters significantly associated with SCA, as continuous variables included larger LV end-diastolic and end-systolic volume indices, elevated BNP, elevated creatinine, larger left atrial volume, lower LVEF, and elevated LV mass index ($p < 0.05$ for each) (Table 3). In addition, SCA was associated with no angiotensin inhibition therapy (23% vs. 9%; $p = 0.02$). Multivariate analysis of these continuous and categorical variables revealed that denervated myocardium remained an independent predictor of time to SCA, in addition to LV end-diastolic volume index, creatinine, and no angiotensin inhibition therapy.

Predictors of risk using optimized cut-points

A post-hoc analysis was performed to determine the optimal cut-point for each of the continuous predictors (Fig. 3). Time to SCA was predicted by greater denervated myocardium (>37.6% of the LV, 19% of subjects), larger LV end-diastolic volume index (cut-point = 99 ml/m^2, 34% of subjects), elevated creatinine (cut-point = 1.49 mg/dl, 26% of subjects) and no angiotensin inhibition therapy (10% of subjects). For example, less denervated myocardium (<37.6% LV) identified a large subgroup (81% of the cohort) at lower risk of SCA [SCA rate of 3.0%/year (95% CI: 1.9% to 4.7%) vs. 10.3%/year (95% CI: 6.2% to 16.1%); $p = 0.001$].

Then we tested how well these dichotomized factors could predict the risk of SCA. Figure 4 shows that the presence of 0, 1, or ≥2 of these risk factors could identify subgroups of subjects having significantly different risks of SCA ($p < 0.001$). Subjects having no high-risk predictor represented 44% of the cohort and had a very low risk of SCA (0.9%/year). In contrast, those with 1 risk factor (36% of the cohort) had an SCA rate of 3.9%/year, and those with 2 or more high risk factors (20% of the cohort) had an annual risk of SCA of 11.7%/year.

Discussion

Our results demonstrate that myocardial sympathetic denervation quantified using ^{11}C-HED PET imaging identifies patients with ischemic cardiomyopathy who are at high risk of SCA. The risk of SCA in this primary prevention population was dependent on the total volume of denervated myocardium and was independent of other imaging parameters, including LVEF,

infarct volume, and hibernating myocardium. Thus, quantifying the extent of myocardial sympathetic denervation may provide a novel approach to identify a subgroup of patients with ischemic cardiomyopathy who would derive the most benefit from a primary prevention ICD.

ICD therapy as a surrogate for aborted arrhythmic death

Currently, there is no consensus regarding which ICD therapies provide an appropriate surrogate for arrhythmic death in observational studies. The device therapies included in our primary endpoint were considerably more restrictive than the prevailing approach in contemporary observational imaging studies, which typically include all appropriate ICD therapies (anti-tachycardia pacing and ICD discharge) (21–23). Appropriate ICD therapies occur at least 3 times as frequently as fatal arrhythmic events (4,18), and self-terminating ventricular arrhythmias may have substrates and triggers that differ from those resulting in arrhythmic death (24). Our prospectively defined primary endpoint was SCA, which included adjudicated arrhythmic death and an ICD equivalent endpoint on the basis of device therapies most clearly associated with lethal ventricular arrhythmias (VF and VT >240 beats/min). In the MADIT II (Second Multicenter Automatic Defibrillator Implantation Trial), the frequency of these device therapies plus death in patients randomized to an ICD (18.3% at 2 years) was similar to the rate of death in the medically treated group (18% at 2 years) (17). Although this analysis supports using these events as surrogates of arrhythmic death in patients with an ICD (17,18), we cannot exclude the possibility that this conservative definition may have underestimated the rate at which arrhythmic death would have occurred in our population.

Myocardial sympathetic innervation and SCA

Recent studies have imaged global cardiac sympathetic innervation in heart failure using ^{123}I-meta-iodobenzylguanidine (MIBG). They have consistently shown an association between reductions in MIBG uptake and endpoints reflecting a variety of composite cardiovascular outcomes in patients with heart failure (21,25–27). However, there is disagreement regarding the preferred imaging parameter (reduced heart-to-mediastinum [H/M] ratio vs. accelerated tracer washout rate) and the added benefit from regional tracer quantification. There is also a paucity of outcome data for cause-specific mortality from SCA.

In a small study of heart failure patients (LVEF <40%; n = 106, 52% ischemic cardiomyopathy), MIBG imaging was shown to predict arrhythmic death, as well as pump failure death and total cardiac mortality (26). Both the H/M ratio and the washout rate predicted arrhythmic death, but only the washout rate and LVEF remained independent after multivariate analysis. In contrast to our study, subjects taking beta-blockers, insulin, or those with significant renal dysfunction at entry were excluded. Thus, more than 97% of our study population would have been excluded, raising questions about generalizing these findings to risk stratification for SCA among contemporary heart failure patients.

A larger observational study (ADMIRE-HF [AdreView Myocardial Imaging for Risk Evaluation in Heart Failure]) imaged 961 subjects with an LVEF ≤35% (66% with ischemic cardiomyopathy) and New York Heart Association functional class II/III heart failure symptoms (27). The composite primary endpoint was heart failure progression (hospitalization or clinical assessment), potentially life-threatening arrhythmias (sustained VT, resuscitated cardiac arrest, or any appropriate ICD therapy including anti-tachycardia pacing), and cardiac death. A late H/M ratio <1.6 (reflecting both denervated myocardium and accelerated washout from increased sympathetic nerve activity) was present in ~80% of patients and predicted the composite endpoint (hazard ratio: 2.5). Evaluating regional

sympathetic innervation and perfusion did not improve this in comparison with the global H/M ratio (27). In contrast, another study evaluating heart failure patients referred for an ICD (n = 116, 74% with ischemic cardiomyopathy) found neither the MIBG H/M ratio nor the washout rate to be predictors of appropriate ICD therapy (21). A semi-quantitative defect score predicted ICD therapy, which is consistent with our findings and supports the importance of quantifying regional sympathetic neuronal function for risk stratification of arrhythmic death (21).

Imaging of myocardial ischemia and infarct volume to predict SCA

Acute myocardial ischemia, fibrosis, and infarction have been demonstrated to be arrhythmogenic substrates. For example, in a large cohort with coronary disease referred for perfusion imaging, the extent of infarction plus ischemia (summed stress perfusion score) was the only independent imaging parameter to predict arrhythmic death (28). This is consistent with our study in that the volume of denervated myocardium approximates the area at risk for ischemia (8,11). Nevertheless, due to our study design and the stable nature of symptoms in our subjects, coronary anatomy was not evaluated, and we did not directly assess the presence or extent of stress-induced ischemia at enrollment. Therefore, the potential roles of inducible ischemia and coronary disease progression in SCA in this study are not defined.

Cardiac magnetic resonance imaging (MRI) has facilitated the quantification of infarct volume, as well as patchy fibrosis (“gray zone”) surrounding the infarct borders. Although cause-specific mortality from arrhythmic death has not been assessed, several studies using MRI have correlated scar volume with cardiac endpoints, including appropriate ICD therapy (22,23,29). Some studies (22), but not all (23,29), have shown that quantification of the “gray zone” improves risk prediction. Interestingly, the MRI “gray zone” is similar in size to viable, denervated myocardium assessed by PET (the difference between denervated and infarcted myocardium). Thus, they may ultimately prove to be assessing a similar substrate with increased risk of lethal arrhythmias. Further studies comparing infarct volume, “gray zone,” and denervated volume will be required to determine whether the 2 approaches provide similar risk stratification for SCA.

Predictive model to assess the risk of SCA

Our post-hoc multivariate analysis demonstrated that quantifying the volume of denervated myocardium along with 3 other variables (LV end-diastolic volume index, creatinine, and angiotensin inhibition therapy) independently predicted arrhythmic risk. Quantifying infarct size, LVEF, and BNP (and other variables) did not improve the predictive model. Although other parameters have been associated with cardiovascular mortality, they either preferentially predict progressive heart failure (as opposed to SCA), or their prognostic information was superseded by the 4 independent factors. Importantly, more than 40% of our study population had none of the risk factors and were at very low risk with an annual SCA rate of <1%. This is actually lower than the rate of arrhythmic death in patients with CAD and an LVEF between 35% and 50%, and these patients are currently not candidates for an ICD. At the other extreme, 20% of our subjects had ≥2 risk factors and a high annual SCA rate of ~12%. A limitation of this analysis relates to its post-hoc nature, inclusion of multiple parameters that could result in overfitting and the optimization of cut-points on a modest sample size. Nevertheless, identification of 4 independent predictors is reasonable in relation to the number of observed events. Further studies will be needed to prospectively validate the model, but because it is independent of ejection fraction among those with moderate-to-severe LV dysfunction, it could ultimately be useful to improve the risk stratification of a much larger number of patients at risk of SCA (6).

Study limitations

Our study specifically excluded patients with recent myocardial infarction, nonischemic cardiomyopathy, and those who had more preserved LV systolic function. Thus, future prospective studies will be required to identify whether PET imaging with ^{11}C-HED can improve risk stratification for SCA in these groups.

Conclusions

Our results indicate that quantifying regional sympathetic denervation with ^{11}C-HED PET may provide a novel approach to identify patients at high risk of arrhythmic death, independent of LVEF. Although PET/computed tomographic scanning is widely available, the use of ^{11}C-HED would be limited to centers in close proximity to a cyclotron. Fortunately, ^{18}fluorine-labeled norepinephrine analogs have a longer half-life that could facilitate broader application (30). With the use of these, molecular imaging of myocardial sympathetic denervation in those patients who have ischemic cardiomyopathy may afford a new approach to improve the targeting of ICDs to those who are at greatest risk of SCA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations and Acronyms

BNP	B-type natriuretic peptide
^{11}C-HED	^{11}C-meta-hydroxyephedrine
^{18}FDG	^{18}F-2-deoxyglucose
ICD	implantable cardiac defibrillator
LV	left ventricle
LVEF	left ventricular ejection fraction
MIBG	^{123}I-meta-iodobenzylguanidine
MRI	magnetic resonance imaging
PET	positron emission tomography
SCA	sudden cardiac arrest
VF	ventricular fibrillation
VT	ventricular tachycardia

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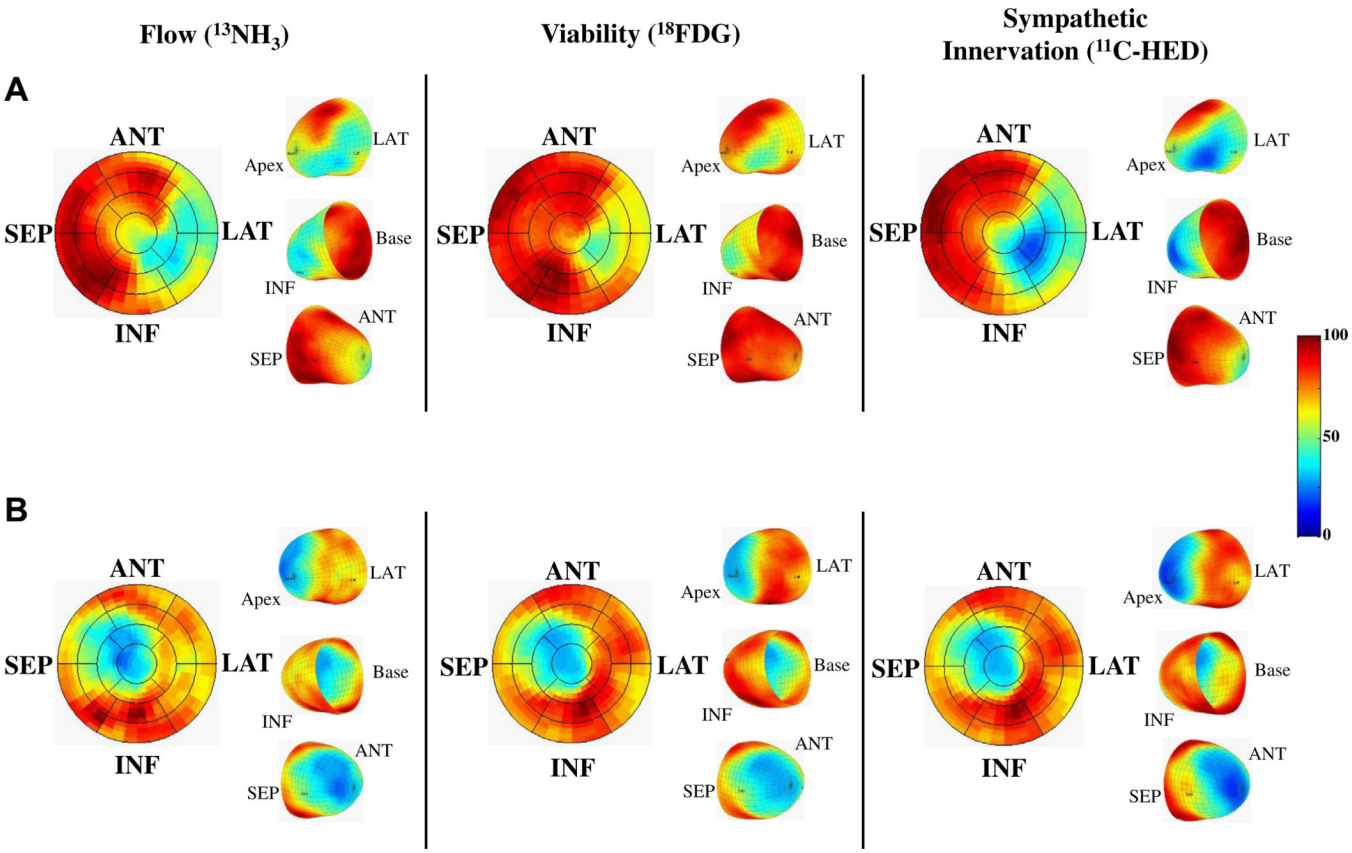

Figure 1. PET imaging of Flow, Viability, and Sympathetic Innervation

(A) A subject experiencing sudden cardiac arrest (SCA). There is a mismatch in infarct size (reduced ^{18}F-2-deoxyglucose [^{18}FDG]), which was smaller than the volume of sympathetic denervation (reduced ^{11}C-meta-hydroxyephedrine [^{11}C-HED]). There was also reduced perfusion (^{13}N-ammonia [$^{13}NH_3$]) with preserved ^{18}FDG indicating hibernating myocardium. In contrast, **B** shows a subject with matched reductions in flow, infarct volume, and sympathetic denervation. ANT = anterior; INF = inferior; LAT = lateral; PET = positron emission tomography; SEP = septum.

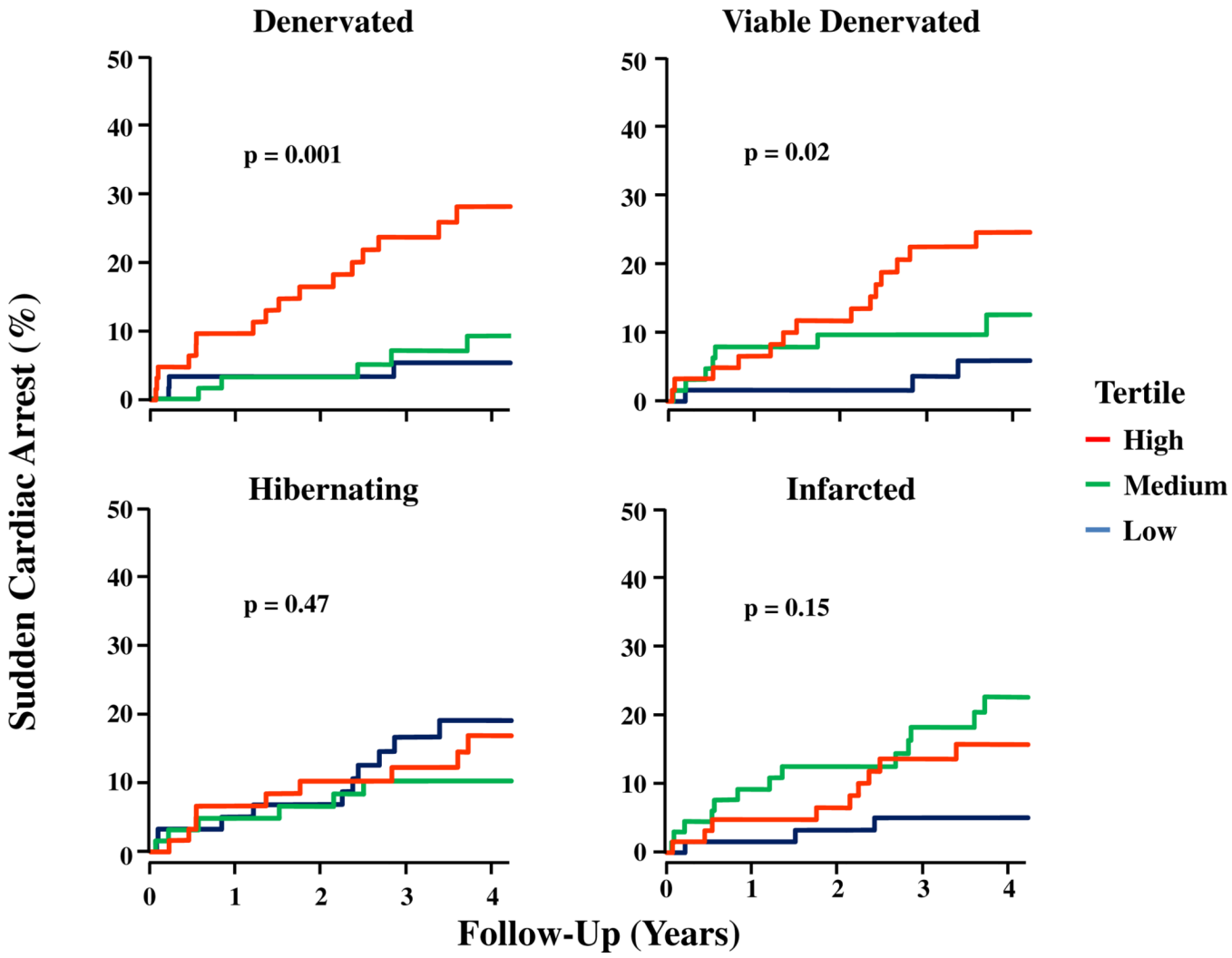

Figure 2. PET Parameters and SCA

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. Abbreviations as in Figure 1.

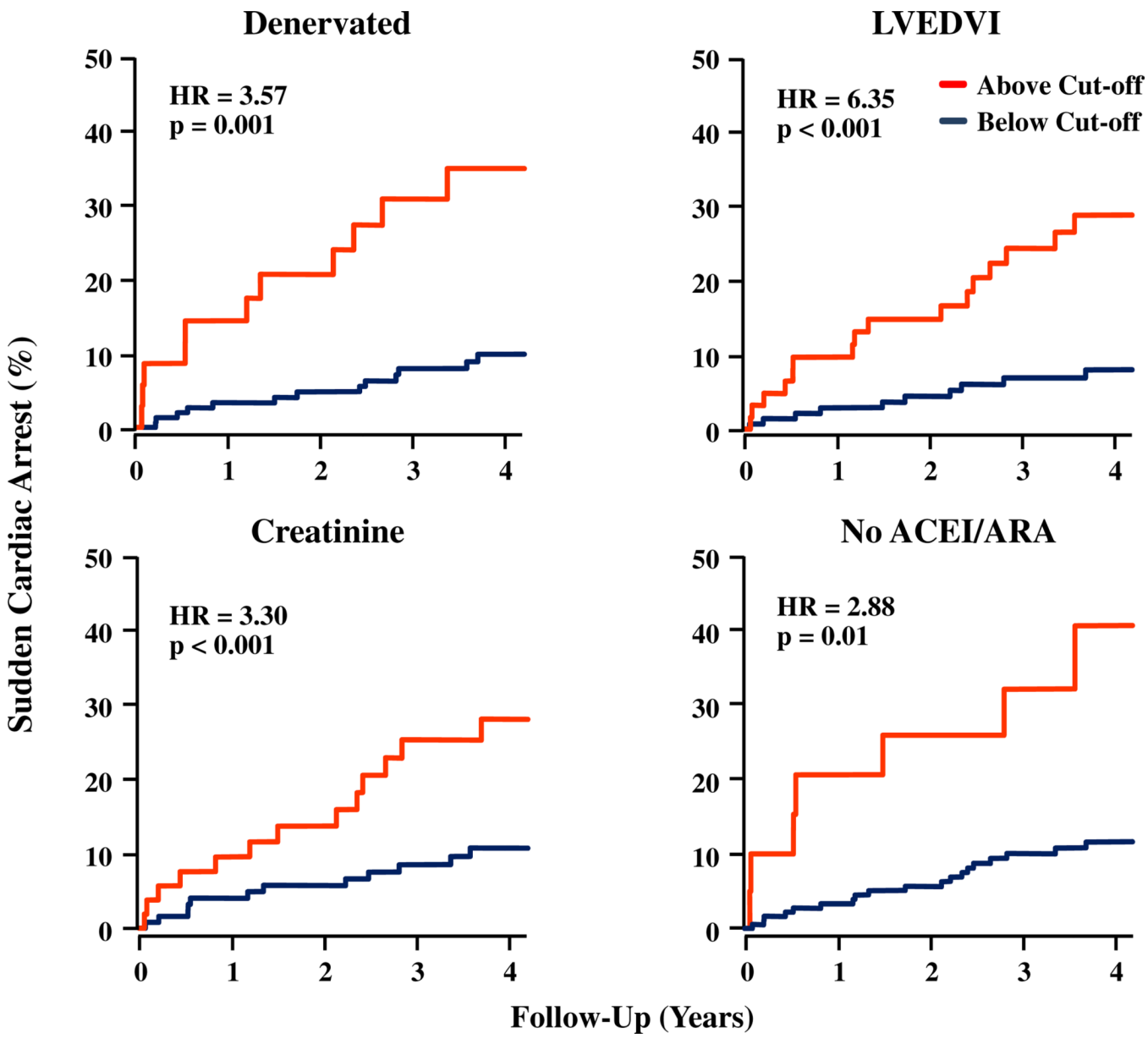

Figure 3. Predictors of SCA by Multivariate Analysis

Kaplan-Meier curves illustrating the incidence of SCA greater than and less than the optimal cut-point for denervated myocardium (>37.6% of left ventricle [LV]), left ventricular end-diastolic volume index (LVEDVI >99 ml/m^2), creatinine (>1.49 mg/dl), and no angiotensin inhibition therapy. The hazard ratio (HR) for each parameter was derived from the multivariate analysis. ACEI/ARA = angiotensin-converting-enzyme inhibitor/angiotensin receptor antagonist. Abbreviations as in Figure 1.

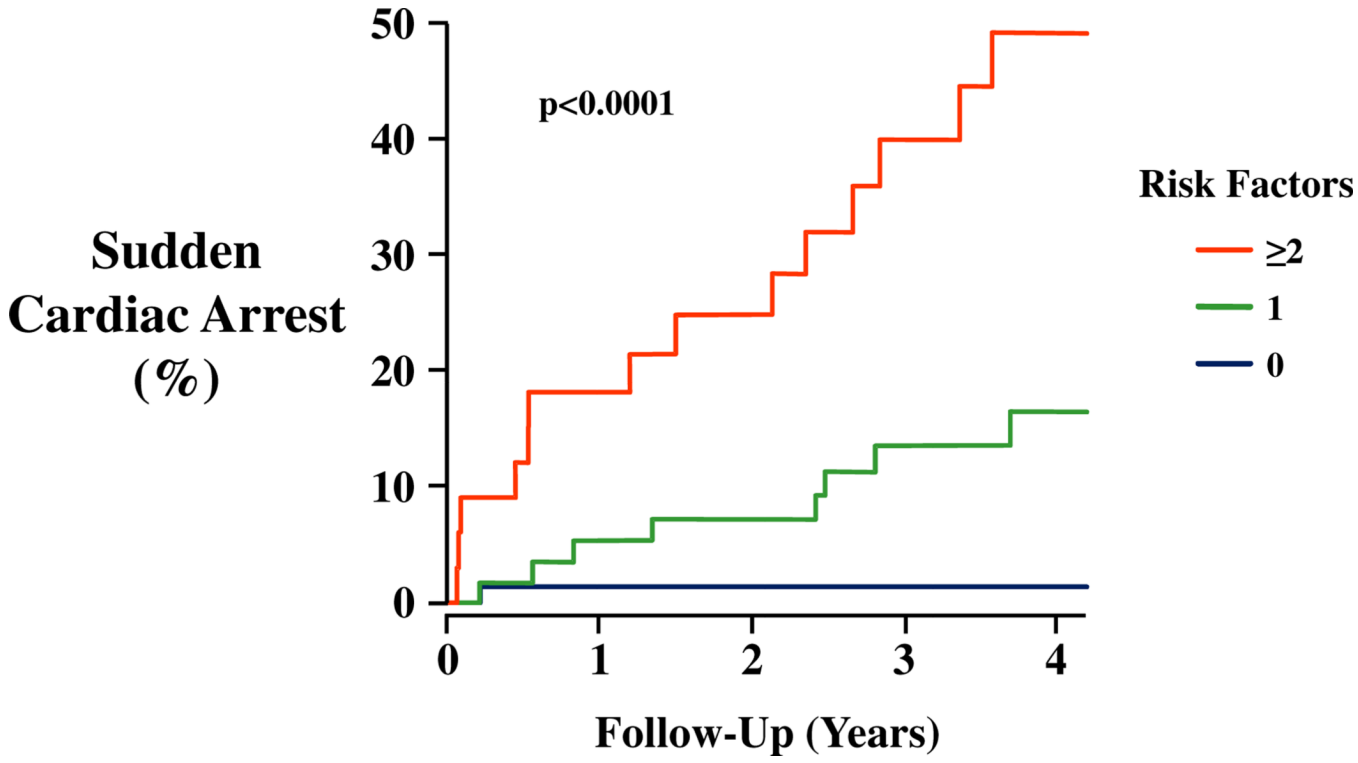

Figure 4. SCA Risk Factor Model

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 2 or more risk factors (red, 20% of cohort), the annual risk of SCA increased to ~12%. Patients with 1 risk factor (green, 36% of cohort) had an intermediate risk of SCA (~4%/year). Abbreviations as in Figure 1.

Table 1

Clinical Parameters and SCA

	SCA (n = 33)	No SCA (n = 171)	p Value
Demographic parameters			
Age (yrs)	66 ± 8	67 ± 12	0.57
Female	0 (0)	21 (12)	0.07
Body mass index (kg/m^2)	28.3 ± 4.5	28.6 ± 5.1	0.76
Body surface area (m^2)	2.1 ± 0.2	2.0 ± 0.2	0.27
NYHA functional class	2.3 ± 0.6	2.1 ± 0.8	0.33
CCS angina class	1.8 ± 0.7	1.8 ± 0.7	0.48
Diabetes mellitus	17 (52)	78 (46)	0.67
Coronary revascularization	21 (64)	138 (81)	0.053
Cardiac rhythm (not sinus)	5 (16)	17 (10)	0.56
QRS duration (ms)	137 ± 32	136 ± 35	0.79
Medications			
Beta-blockers	32 (97)	163 (95)	0.97
Amiodarone	3 (9)	16 (9)	0.78
Antiplatelet agents or warfarin	32 (97)	169 (99)	0.98
Angiotensin inhibition therapy	26 (79)	157 (92)	0.052
Aldosterone antagonists	14 (42)	67 (39)	0.88
Digoxin	13 (39)	66 (39)	0.91
Hemodynamic parameters			
Systolic blood pressure (mm Hg)	127 ± 17	126 ± 21	0.93
Heart rate (beats/min)	63 ± 11	66 ± 12	0.23
Rate pressure product (beats/min · mm Hg)	7,952 ± 1,389	8,398 ± 2,282	0.28
Laboratory parameters			
Hematocrit (%)	39.3 ± 5.3	41.0 ± 5.8	0.11
Potassium (mEq/l)	4.3 ± 0.6	4.3 ± 0.4	0.83
Sodium (mEq/l)	139 ± 3	139 ± 3	0.26
Creatinine (mg/dl)	1.7 ± 1.2	1.3 ± 0.7	0.04
B-type natriuretic peptide (ng/l)	741 ± 694	412 ± 479	0.001

Values are mean ± SD or n (%).

CCS = Canadian Cardiovascular Society; NYHA = New York Heart Association; SCA = sudden cardiac arrest.

Table 2

Imaging Parameters in Subjects With SCA

	SCA (n = 33)	No SCA (n = 171)	p Value
PET parameters (% LV)			
Denervated myocardium	33 ± 10	26 ± 11	0.001
Infarcted myocardium	22 ± 7	19 ± 9	0.18
Viable, denervated myocardium	10 ± 6	7 ± 5	0.02
Hibernating myocardium	3 ± 2	3 ± 3	0.50
Echocardiography			
LV ejection fraction (%)	24 ± 8	28 ± 9	0.053
LV end-diastolic volume index (ml/m^2)	107 ± 28	86 ± 30	<0.001
LV end-systolic volume index (ml/m^2)	81 ± 21	63 ± 26	<0.001
LV mass index (g/m^2)	167 ± 37	150 ± 48	0.07
Mitral regurgitation	2.0 ± 1.2	1.6 ± 1.1	0.04

Values are mean ± SD.

LV = left ventricle; SCA = sudden cardiac arrest.

Table 3

Significant Predictors of Time to SCA

	Univariate		Multivariate	
Variable	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**p Value**
PET parameters (per 1% of LV)				
Denervated myocardium	1.057 (1.023–1.092)	0.001	1.069 (1.023–1.117)	0.003
Viable, denervated myocardium	1.067 (1.008–1.130)	0.025		
Infarcted myocardium	1.029 (0.990–1.069)	0.15		
Hibernating myocardium	0.950 (0.822–1.099)	0.49		
Other significant parameters				
LVEDV index (per ml/m^2)	1.021 (1.011–1.032)	<0.0001	1.030 (1.010–1.050)	0.003
LVESV index (per ml/m^2)	1.022 (1.011–1.033)	<0.0001		
BNP (per ng/L)	1.001 (1.000–1.001)	0.0003		
Creatinine (per mg/dl)	1.53 (1.21–1.95)	0.0005	2.30 (1.12–4.71)	0.023
LA volume (per ml)	1.011 (1.003–1.019)	0.010		
No angiotensin inhibition therapy	2.88 (1.25–6.67)	0.014	4.31 (1.07–17.38)	0.040
LV ejection fraction (per 1%)	0.951 (0.913–0.990)	0.016		
LV mass index (per g/m^2)	1.007 (1.000–1.014)	0.038		

BNP = B-type natriuretic peptide; CI = confidence interval; HR = hazard ratio; LA = left atrial; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; PET = positron emission tomography; SCA = sudden cardiac arrest.