Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 63, No. 2, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.07.096

Cardiac Imaging

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

James A. Fallavollita, MD,*†‡ Brendan M. Heavey, MPH,† Andrew J. Luisi, Jr, MD,†‡§ Suzanne M. Michalek, MS,† Sunil Baldwa, MBBS,*†‡ Terry L. Mashtare, Jr, PhD,|| Alan D. Hutson, PhD,|| Robert A. deKemp, PhD,¶ Michael S. Haka, PhD,§ Munawwar Sajjad, PhD,§ Thomas R. Cimato, MD,†‡ Anne B. Curtis, MD,‡ Michael E. Cain, MD,‡# John M. Canty, Jr, MD*†‡#**

Buffalo, New York; and Ottawa, Ontario, Canada

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 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) (J Am Coll Cardiol 2014;63:141–9) © 2014 by the American College of Cardiology Foundation

Numerous clinical and demographic variables have been associated with an increased risk of arrhythmic death, and many electrophysiological approaches have been proposed

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From the *VA Western New York Health Care System, Buffalo, New York; †Center for Research in Cardiovascular Medicine, University at Buffalo, Buffalo, New York; ‡Department of Medicine, University at Buffalo, Buffalo, New York; §Department of Nuclear Medicine, University at Buffalo, Buffalo, New York; ||Department of Biostatistics, University at Buffalo, Buffalo, New York; #Department of Biomedical Engineering, University at Buffalo, Buffalo, New York; **Department of Physiology and Biophysics, University at Buffalo, Buffalo, New York; and the ¶Cardiac PET Centre, University of Ottawa Heart Institute, Ottawa, Ontario, Canada. This research was supported by the U.S. National Institute of Health Heart, Lung, and Blood Institute (grant no. HL-76252). Dr. Haka is currently employed by Siemens Medical. Dr. Curtis has served as a consultant or received research grants or honoraria from Medtronic, Inc. and St. Jude Medical; and served on the advisory board of Bristol-Myers Squibb, Pfizer, Inc., Janssen Pharmaceuticals, Daiichi Sankyo, and Biosense Webster. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received March 8, 2013; revised manuscript received July 4, 2013, accepted July 8, 2013.

JACC Vol. 63, No. 2, 2014
January 21, 2014:141–9

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

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) [241 MBq] 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 FlowQuant (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