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Electrocardiographic predictors of sudden and non-sudden cardiac death in patients with ischemic cardiomyopathy

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ABSTRACT

Objective: This study evaluated the prognostic value of electrocardiogram (ECG)-based predictors in the primary prevention of sudden cardiac arrest (SCA) among ischemic cardiomyopathy patients with depressed left ventricular ejection fraction (LVEF ≤35%).
Background: The prediction of cause-specific mortality in high-risk patients offers the potential for targeting specific therapies (i.e., implantable cardioverter-defibrillator [ICD]).
Methods: Subjects were recruited from the *Prediction of Arrhythmic Events with Positron Emission Tomography* (PAREPET) study. Continuous Holter 12-lead ECG recordings were obtained at the start of study and used to compute 15 clinically-important ECG abnormalities (e.g., atrial fibrillation).
Results: Among 197 patients (age 67 ± 11 years, 93% male, mean follow-up 4.1 years) enrolled, 30 (15%) were SCA cases and 35 (18%) cardiac non-sudden deaths (C/NS). In multivariate analysis, only heart-rate-corrected QT interval (QTc) predicted SCA (hazard ratio 2.9 [1.2–7.3]) and only depressed heart rate variability (HRV) predicted C/NS (hazard ratio 5.0 [1.5–17.1]) independent of demographic and clinical parameters.
Conclusions: Among patients with depressed LVEF, prolonged QTc suggests greater potential benefit from ICD therapy to prevent SCA; depressed HRV suggests potential benefit from bi-ventricular pacing to prevent C/NS.

Introduction

Non-invasive risk stratification to identify and manage high-risk populations is a clinical priority.[1] Fatal tachyarrhythmias (i.e., sustained ventricular tachycardia [VT] or ventricular fibrillation [VF]) and heart failure complications are very common in patients with ischemic cardiomyopathy, which can lead to sudden cardiac death (SCD) or cardiac non-sudden death (C/NS), respectively. Secondary prevention of fatal complications in ischemic cardiomyopathy emphasizes (1) early termination of VT/VF using implantable cardioverter-defibrillator (ICD) shocks after successful resuscitation from sudden cardiac arrest (SCA) or (2) aggressive treatment using bi-ventricular (BiV) pacing for cardiac resynchronization to prevent heart failure mortality in selected high-risk patients. Elaborate guidelines advocate not only the use of a differential approach according to multiple diagnostic parameters, but also the consideration of the clinical status of the patient in order to risk-stratify different cardiac populations. Nevertheless, depressed left ventricular ejection fraction (LVEF) remains the only clinically-used tool to identify ischemic cardiomyopathy patients at the greatest risk for SCA or C/NS and, therefore, most in need of preventive treatment. This limited-sensitivity approach, which primarily relies on LVEF to identify those who will benefit the most from targeted

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ICD or BiV pacing, has been found to be fallible in the prevention of SCA or C/NS.[2,3] Continued efforts for accurate risk stratification are still warranted in ischemic cardiomyopathy.

The 12-lead electrocardiogram (ECG) is widely known to provide valuable prognostic information in different cardiac populations and widely used as an easily accessible and noninvasive diagnostic tool.[4,5] The value of the ECG in predicting cardiac events has been repeatedly assessed and validated in many clinical populations. In particular, abnormalities seen on standard 10 s, 12-lead ECG strips (referred to as resting ECG parameters) have been described as promising clinical tools to predict cardiovascular death.[6] In addition, abnormalities seen during continuous Holter ECG recordings (e.g., ST segment monitoring and transient tachyarrhythmia alarms) have been previously described to provide more insights about the pathogenesis of cardiovascular death.[7] Despite the abundant literature concerning the value of resting and continuous Holter ECG parameters in post-acute myocardial infarction patients,[8,9] limited data exist on the prognostic value of these parameters in ischemic cardiomyopathy patients who are deemed eligible, according to their LVEF, for ICD therapy for the secondary prevention of SCA. Evaluating the incremental value of the resting and continuous Holter ECG, beyond that of the LVEF, might improve the optimal targeting of ICD and other more invasive therapies in high-risk cardiac populations.

We have previously reported[10] that the ubiquitous presence of ECG confounders (i.e., pacing, left bundle branch block [LBBB], QRS widening, and atrial fibrillation) among chronic heart failure patients substantially interferes with the interpretation of the ECG. A classic example of this interference in the ECG literature is the inability to evaluate ST deviation in the presence of LBBB. Previous reports have excluded patients with interpretation confounders from further analysis,[11] which limits the clinical value of many important ECG parameters for widespread clinical utility. Evaluating the presence or absence of ECG confounders as potential markers of risk, rather than excluding patients with such confounders, could provide a tool to account for the role of confounders that preclude all means of analyzing important ECG parameters. In this study, we sought to determine the prognostic value of resting and continuous Holter ECG parameters, in relation to presence of ECG confounders, for cause-specific mortality in subjects with ischemic cardiomyopathy who were eligible for the secondary prevention of SCA with ICD therapy.

Methods

Setting and subjects

Patients for this study were recruited from an NIH-funded study known as *Prediction of Arrhythmic Events with Positron Emission Tomography* (PAREPET). The PAREPET study was prospective in nature and designed to determine whether or not denervated or hibernating myocardium assessed with positron emission tomography could predict SCA among subjects with ischemic cardiomyopathy who were eligible for ICD therapy (pre-enrollment LVEF $<$ 35% for Class II–VI and $<$30% for Class I).[12] Therefore, enrolled subjects exhibited coronary artery disease, pre-enrollment LVEF less than or equal to 35%, and New York State Heart Association Functional Class (NYHA) I–III heart failure symptoms. Although all patients were clinically eligible for ICD therapy, only 81% had an ICD implanted prior to a coronary event. The study design and methods featured in PAREPET have been reported in detail.[13] In short, patients eligible for PAREPET first underwent a baseline echocardiogram, PET scan, and 24 h continuous Holter ECG recording. Next, they received follow-up assessment by phone in 3-month intervals. There were no modifications to the standard care received by enrollees. Patients reporting ICD shocks were seen in a clinic where they had their ICDs interrogated. Medical records of patients meeting any study endpoints (i.e., SCA or C/NS) were collected and reviewed periodically. The PAREPET study complies with the Declaration of Helsinki and was approved by the appropriate institutional review boards. All subjects included in the PAREPET study consented to participate.

Endpoints and clinical data

Our analysis included consecutive outpatients from the PAREPET study ($n = 197$). Those who were lost to follow up ($n = 1$) or did not complete continuous Holter ECG monitoring ($n = 6$) were not included in our analysis. Clinical data were collected from electronic medical charts at the beginning of the study that included clinical presentation, past medical history, medications, and laboratory and other diagnostic tests. Endpoints were screened at regular intervals and were classified using modified Hinkle-Thaler criteria.[14,15] The primary endpoint was SCA, which was defined as either arrhythmic death (i.e., abrupt collapse with pulse cessation without prior

Table 1
The definitions of high-risk ECG parameters used in this study.

#	ECG parameter	Definition
1	QRS duration[1]	Duration from QRS onset to QRS offset averaged among all leads over 10 s
2	Heart-rate corrected QT interval[1]	Duration from QRS onset to T offset averaged among all leads over 10 s then corrected for heart rate using Bazzett's formula ($QT/RR^{1/2;}$)
3	Fragmented QRS[18]	(1) RSR morphology $\geq$ 2 R′ or (2) notching in the nadir of S wave with a narrow QRS ($<$120 ms) or (3) $\geq$ 2 R′ or $\geq$ 2 notches in the nadir of S wave with a widened QRS
4	Q waves[19]	The presence of pathologic Q waves ($>$40 ms) in at least two leads corresponding to the same coronary territory
5	Left bundle branch block[6]	The presence of this pattern as per American Heart Association guidelines
6	Left ventricular hypertrophy[6]	The presence of this pattern as per Cornell voltage criteria
7	Spatial QRS-T angle[20]	The three-dimensional spatial angle between the mean R and T vectors estimated directly from the 12-lead ECG
8	Minimum heart rate[21]	The minimum 5 min averaged heart rate during the 24 h Holter monitoring period
9	Heart rate variability[1]	The standard deviation of normal-to-normal R–R intervals of all R–R intervals averaged over 24 h
10	Atrial fibrillation[6]	A heart rhythm with irregular RR interval with absent P wave at any time during the 24 h Holter recording
11	Non-sustained ventricular tachycardia[1]	At least one episode of $\geq$3 consecutive ventricular beats at a rate of $\geq$120 beats/minute
12	Ventricular ectopic activity[21]	The presence of frequent premature ventricular contractions at rate of $\geq$10/hour for the duration of the Holter recording
13	ST depression[22]	The presence of at least one episode of ST depression of $\geq$0.5 mm in leads V2–V3 or $\geq$1 mm in all other leads in $\geq$2 contiguous leads for at least 5 min at any time during the Holter recording
14	QT/RR slope[23]	The linear regression slope between all beat-to-beat QT and R–R intervals over a 24 h period
15	Persistent pacing[24]	100% of the total monitoring period with prolonged QRS complexes due to single chamber right ventricular (RV) pacemaker spikes. Bi-ventricular pacing, although it limits the interpretation of other ECG parameters, was not considered a high-risk parameter.