Beat-to-beat three-dimensional ECG variability predicts ventricular arrhythmia in ICD recipients

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BACKGROUND Methodological difficulties associated with QT measurements prompt the search for new electrocardiographic markers of repolarization heterogeneity.

OBJECTIVE We hypothesized that beat-to-beat 3-dimensional vectorcardiogram variability predicts ventricular arrhythmia (VA) in patients with structural heart disease, left ventricular systolic dysfunction, and implanted implantable cardioverter-defibrillators (ICDs).

METHODS Baseline orthogonal electrocardiograms were recorded in 414 patients with structural heart disease (mean age 59.4 ± 12.0; 280 white [68%] and 134 black [32%]) at rest before implantation of ICD for primary prevention of sudden cardiac death. R and T peaks of 30 consecutive sinus beats were plotted in 3 dimensions to form an R peaks cloud and a T peaks cloud. The volume of the peaks cloud was calculated as the volume within the convex hull. Patients were followed up for at least 6 months; sustained VA with appropriate ICD therapies served as an end point.

RESULTS During a mean follow-up time of 18.4 ± 12.5 months, 61 of the 414 patients (14.73% or 9.6% per person-year of follow-up) experienced sustained VA with appropriate ICD therapies: 41 of them were white and 20 were black. In the multivariate Cox model that included inducibility of VA and use of beta-blockers, the highest tertile of T/R peaks cloud volume ratio significantly predicted VA (hazard ratio 1.68, 95% confidence interval 1.01 to 2.80; $P = .046$) in all patients. T peaks cloud volume and T/R peaks cloud volume ratio were significantly smaller in black subjects (median 0.09 [interquartile range 0.04 to 0.15] vs. median 0.11 [interquartile range 0.06 to 0.22], $P = .002$).

CONCLUSION A relatively large T peaks cloud volume is associated with increased risk of VA in patients with structural heart disease and systolic dysfunction.

KEYWORDS Ventricular arrhythmia; Risk stratification; Vectorcardiogram; Variability; Repolarization

ABBREVIATIONS 3D = three-dimensional; **CI** = confidence interval; **CL** = cycle length; **ECG** = electrocardiogram; **HF** = heart failure; **HR** = hazard ratio; **HRm** = heart rate mean; **HRv** = heart rate variance; **ICD** = implantable cardioverter-defibrillator; **MTWA** = microvolt T-wave alternans; **NYHA** = New York Heart Association; **QTm** = QT interval mean; **QTv** = QT variance; **QTVI** = QT Variability Index; **VA** = ventricular arrhythmia; **VCG** = vectorcardiogram; **VT** = ventricular tachycardia

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In large randomized clinical trials, implantable cardioverter-defibrillators (ICDs) have been proven to provide survival benefit[1–3] for heart failure (HF) patients with systolic dysfunction. White men compose the majority (70% to 85%) of study populations in clinical trials.[4,5] The *Get With the Guidelines* program and Medicare and Medicaid data show that ICD therapy is underutilized in black subjects.[5] On the other hand, some studies have suggested that black subjects might not benefit from ICDs to the same extent as white subjects,[6,7] but the data are inconclusive.[8] Race-specific guidelines for risk stratification of ventricular arrhythmia (VA) are needed; however, race-specific differences are not well described.

Increased temporal repolarization lability is recognized as a marker of susceptibility to VA. Different approaches to the assessment of temporal lability of repolarization have been proposed and used. Although metrics of spatial dispersion of repolarization vary in terms of the studied repolarization parameter (T-wave width,[9] the total cosine R-to-T descriptor and total morphology dispersion,[10] T-wave shape indexes,[11] T peak–T end interval[12]), methods of assessment of temporal heterogeneity of ventricular repolarization have been largely confined to the assessment of temporal QT variability, although methodological difficulties associated with QT measurements were previously shown.

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Increased QT variability measured on surface electrocardiogram (ECG),[13] as well as increased intracardiac repolarization lability.[14] is associated with higher risk of sustained VA. Previously, gender differences in repolarization lability were shown in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) study population,[15] but racial differences were not explored. We hypothesized that measured in 3 dimensions, beat-to-beat vectorcardiogram variability predicts VA in patients with structural heart disease, systolic dysfunction, and implanted ICD, and it may be helpful in studying racial differences.

Methods

The study protocol was approved by the Johns Hopkins University internal review board, and all patients gave written informed consent before entering the study.

Study population

This report presents a data analysis of the first consecutive 414 participants in the Prospective Observational Study of the ICD in Sudden Cardiac Death Prevention (PROSE-ICD) study with at least 6 months of follow-up, recruited at the Johns Hopkins Hospital site. PROSE-ICD (NCT00733590) is an ongoing prospective observational multicenter cohort study of primary prevention ICD patients with structural heart disease. Patients with ischemic (myocardial infarction at least 4 weeks old) or nonischemic cardiomyopathy (at least 9 months), an ejection fraction ≤35%, and stable New York Heart Association (NYHA) class II-III heart failure symptoms on optimal heart failure medications were enrolled. NYHA class I patients were included if they fulfilled MADIT II criteria: ischemic cardiomyopathy with left ventricular ejection fraction ≤30%. Patients were excluded if the ICD was indicated for secondary prevention of sudden cardiac arrest, if they had a permanent pacemaker or a class I indication for pacing, or if they were pregnant.

Surface ECG recording and analysis

A baseline modified Frank orthogonal XYZ leads ECG was recorded before ICD implantation during 5 minutes at rest by Personal Computer - based Electrocardiograph PC ECG machine (Norav Medical Ltd, Thornhill, Ontario, Canada) with a 1,000-Hz sampling frequency.

The ECG was considered eligible for repolarization lability analysis if it was recorded at sinus rhythm and the number of excluded beats (premature ventricular or atrial complexes and noisy beats) did not exceed 15% of the epoch. Temporal beat-to-beat QT variability during sinus rhythm was measured automatically as previously described.[16] The heart rate mean (HRm) and heart rate variance (HRv) and the QT interval mean (QTm) and QT interval variance (QTv) were computed from the respective time epochs (3 to 5 min). A normalized QT variability index (QTVI) was derived according to the equation: $QTVI = \log_{10}[(QTv/QTm^2)/(HRv/HRm^2)]$. All 3 orthogonal leads were analyzed separately, and then average QT variability values were calculated across XYZ leads. The microvolt T-wave alternans (MTWA)[17,18] was measured spectrally by custom-designed MATLAB (MathWorks, Inc., Natick, Massachusetts) software. The MTWA test was considered positive if the absolute voltage of T-wave alternation was ≥1.9 μV with MTWA exceeding noise at least 3 times (K score ≥3).

Three-dimensional (3D) ECG variability analysis: the volume of R and T peaks clouds

Methodology of analysis was previously described.[19] Baseline wander was corrected with a zero or first-order polynomial fit. In sinus rhythm ECG, 30 consecutive sinus beats were selected, and premature ventricular complexes were manually excluded. The peaks of R-waves and T-waves were detected automatically in 3D ECG through use of custom-designed software written in MATLAB. The peak of R-waves was found as the furthest point away from the origin of the 3 loops (Figure 1). The peak of T-waves was detected automatically as the farthest point away from the origin in a time frame following the detected R-wave peak. The 3D ECG variability analysis was performed by an investigator blinded to the study outcomes (L.H.). Results were independently reviewed by two investigators (L.H and L.G.T.) to ensure accuracy and quality of peaks detection. R and T peaks were plotted in 3D to form an R peaks cloud

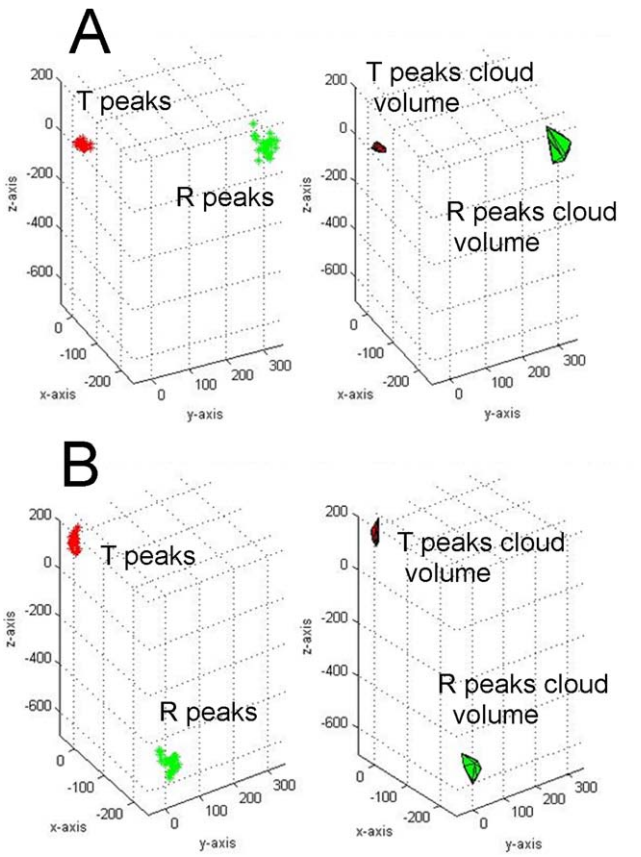

Figure 1 Representative baseline T/R peaks cloud volumes in a patient without **(A)** and one with **(B)** subsequent sustained ventricular tachyarrhythmia and appropriate ICD therapy at follow-up. ICD = implantable cardioverter-defibrillator.