Interlead Heterogeneity of R- and T-Wave Morphology in Standard 12-Lead ECGs Predicts Sustained Ventricular Tachycardia/Fibrillation and Arrhythmic Death in Patients with Cardiomyopathy

Short Title: Interlead RWH and TWH Predict VT/VF

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* In Memoriam: The authors are grateful for Dr. Josephson’s inspiring guidance and contributions to this study.

Dr. Tan receives research grants from the American Heart Association (AHA-SDG 16FDG31280012), Boston Scientific, and Biotronik. Drs. Nearing and Verrier are inventors of the method employed for analysis of R-wave and T-wave heterogeneity, with patent assigned to Beth Israel Deaconess Medical Center. Other authors: No disclosures.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jce.13288.

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ABSTRACT

Introduction. Nonuniformities in depolarization and repolarization morphology are critical factors in ventricular arrhythmogenesis.

Methods and Results. We assessed interlead R-wave and T-wave heterogeneity (RWH, TWH) in standard 12-lead electrocardiograms using second central moment analysis. This technique quantifies variance about the mean morphology of beats in adjoining precordial leads, V4, V5, and V6. The study was conducted in 120 consecutive patients without an apparent reversible trigger for VT, recent myocardial infarction, or active ischemia, who presented for electrophysiologic study, implantable cardioverter defibrillator (ICD) placement, or generator change at our institution from 2008 to 2011. Primary outcome was sustained VT/VF or appropriate ICD therapies. Secondary outcome was arrhythmic death or resuscitated cardiac arrest. Cutpoints for elevated RWH (>160 μV) and TWH (>80 μV) identified 69% of primary outcome cases and 85% of secondary outcome cases. Cardiomyopathy patients who met the primary outcome (n=42) had significantly higher TWH than those who did not (n=28) (TWH: 95±11 vs. 44±9 μV, p<0.002). Likewise, cardiomyopathy patients who met secondary outcome (N=13) had VT/VF during follow-up and also had significantly higher TWH than survivors (N=57) (TWH: 105±24 vs. 67±8μV, p<0.002). Kaplan-Meier analysis revealed significant differences in arrhythmia-free survival (p=0.012) and total survival (p=0.011) among cardiomyopathy patients with (n=37) compared to without (n=33) elevated RWH and/or TWH independent of age, sex, and left ventricular ejection fraction (LVEF).

Conclusion. Interlead RWH and TWH in 12-lead ECGs predict sustained ventricular arrhythmia, appropriate ICD therapies, and arrhythmic death or cardiac arrest in cardiomyopathy patients independent of LVEF and other standard variables.
Keywords: Heterogeneity, Arrhythmia, Ventricular Tachycardia, Cardiomyopathy, ECG, sudden cardiac death

Abbreviations:
ECG = electrocardiogram
EP = electrophysiologic
ICD = implantable cardioverter/defibrillator
LVEF = Left ventricular ejection fraction
RWH = R-wave heterogeneity
SCD = sudden cardiac death
SVT = supraventricular tachycardia
TWA = T-wave alternans
TWH = T-wave heterogeneity
VF = ventricular fibrillation
VT = ventricular tachycardia

INTRODUCTION
Sudden cardiac death (SCD) is a leading cause of cardiovascular mortality with ~299,000 adult out-of-hospital deaths annually in the United States (1). Implantable cardioverter/defibrillators (ICDs) have emerged as the main tool for primary prevention of SCD (2), are prescribed for patients with low left ventricular ejection fraction (LVEF) and heart failure, and have produced a 7.9% reduction in absolute mortality (3). However, a majority of SCD events occurs in patients with preserved or only mildly impaired LVEF (4,5). These data underscore the importance of accurate identification of appropriate candidates for ICD implantation. Although LVEF remains the single most important marker
of vulnerability to ventricular arrhythmia, it is an imprecise predictor at best, in part because it does not fully probe the complex electroanatomic substrates that predispose to ventricular arrhythmias.

We tested the capacity for arrhythmia risk stratification of a novel method known as second central moment analysis to detect interlead heterogeneity of both depolarization and repolarization morphology simultaneously from standard 12-lead ECG recordings (6,7). The technique is sufficiently sensitive to detect premonitory electrophysiological changes prior to the onset of nonsustained ventricular tachycardia (VT) in hospitalized patients with decompensated heart failure (8). In that study, crescendos in R-wave and T-wave heterogeneity (RWH and TWH) preceded the appearance of microvolt T-wave alternans (TWA) followed by VT. These findings underscored the mechanistic linkages among interlead ECG morphology heterogeneity, TWA (9), and VT. In 5600-subject Health Survey 2000, elevated RWH, J-wave heterogeneity (JWH), and TWH were associated with 3.2-fold increased risk for sudden cardiac death following multivariable adjustment (10). However, the association of RWH and TWH with sustained ventricular arrhythmias remained unclear.

We therefore investigated whether interlead heterogeneity of both depolarization and repolarization morphology is associated with sustained VT/VF, appropriate ICD therapy, or death in consecutive patients with compared to without cardiomyopathy. Importantly, RWH and TWH testing was performed from 12-lead ECGs recorded at rest during the routine flow of clinical activity.

METHODS

Study Population and Design
The study protocol was approved by the Institutional Review Board of Beth Israel Deaconess Medical Center (BIDMC), Boston, MA. The study group consisted of 120 consecutive patients with technically successful continuous 12-lead ECG recordings who presented to BIDMC for electrophysiologic (EP) study, VT ablation, ICD implantation, or generator change between January 2008 and December 2011. Patients with an apparent reversible trigger for VT, including those with congestive heart failure or electrolyte abnormalities and active coronary artery ischemia, were excluded from analysis. Thus, the study group for the primary analysis (N=70) consisted of cardiomyopathy patients (LVEF <50%) with (N=42) or without sustained VT/VF (N=28). For comparison, we also analyzed interlead ECG heterogeneity in a group of patients (N=50) without cardiomyopathy who had either idiopathic VT (N=15) or supraventricular tachycardia (SVT) (N=35).

Cardiomyopathy was determined to be due to coronary artery disease if there was regional wall motion abnormality and/or scar on echocardiography, cardiac magnetic resonance imaging, or nuclear stress imaging that was consistent with prior infarction, and any of the following criteria were met: 1) documented prior myocardial infarction; 2) >70% stenosis of a major epicardial coronary artery; 3) history of coronary artery bypass graft surgery; 4) history of percutaneous coronary revascularization. All other patients with cardiomyopathy were deemed to have a nonischemic etiology. LVEF was assessed by transthoracic echocardiography (General Electric, Inc., Hartford CT) or cardiac magnetic resonance imaging (Phillips Medical Systems, Amsterdam, Netherlands). Left ventricular hypertrophy was defined as left ventricular mass index ≥131 g/m² or wall thickness >1.2 cm.

Patients were followed over 31 months (mean; range: <1-168 months); 93% of cardiomyopathy patients were followed at 3- to 6-month intervals. The remaining 5
cardiomyopathy patients had infrequent follow-up but at least 2 visits (range 2-5) over 46 months. The primary outcome was occurrence of sustained VT or ventricular fibrillation (VF), which was defined as lasting >30 seconds or requiring cardioversion or ICD antitachycardia therapy, and was established by reviewing medical records. The secondary outcome was cardiovascular mortality including resuscitated cardiac arrest and was based on medical and public health records.

**ICD Detection Criteria**

ICD antitachycardia therapy detection was programmed to suit individual patient needs according to physician judgment. Inappropriate ICD therapy was defined as therapy delivered for atrial tachyarrhythmia or extraneous potentials generated by other cardiac or extracardiac signals. There was no significant difference in ICD tachycardia programming among patients with or without appropriate ICD therapy.

**ECG Recording**

Continuous 12-lead ECGs were acquired with standard filtering (0.05-150 Hz) using Cardiolab GE Prucka (GE Healthcare, Inc., Milwaukee WI) at a sampling rate of 1000 samples/sec per channel with a 16-bit A/D converter and an LSB resolution of 1.5 microvolt. Patients were supine at rest prior to any EP study or procedure. Antiarrhythmic therapy (amiodarone, sotalol or dofetilide) was received by 29% cardiomyopathy patients at the time of study.

**Second Central Moment Analysis**

Interlead depolarization and repolarization morphology heterogeneity was assessed from 3-min ECG segments by an investigator blinded to clinical status and outcomes using second
central moment analysis (6,7, technical appendix) (Fig. 1). This method quantifies the variability about the mean morphology of adjoining leads ($V_4$, $V_5$, and $V_6$ in this study) on a beat-to-beat basis. Specifically, after the signals are processed to filter noise and remove baseline wander, the software generates a mean waveform separately for the QRS and T waves (to include the J point and entire T wave) of the adjoining precordial leads, which were identified by the MARS commercial software (GE Healthcare, Milwaukee WI). This mean interlead morphology constitutes the first moment or central axis in the terminology of Newtonian physics. The second central moment, or mean-square deviation, was then determined to quantify the variability or splay about the mean morphology. Finally, the maximum square root of the second central moment was calculated to obtain the heterogeneity values in microvolts. The measurements were made on a beat-to-beat basis and the results were averaged for each 15-sec epoch. Thus, RWH and TWH are quantitative estimates of the interlead splay (the second moment) about the mean R- and T-wave morphologies (the first moment) and are automatically reported by the computational algorithms.

Using this analytic technique, heterogeneity measurement is not unduly weighted by protracted termination or inflections in the waveforms, ST-segment changes, or presence of U waves, features that limit accurate dispersion measurement by conventional analyses. Leads $V_4$, $V_5$, and $V_6$ were chosen for analysis because of their low intrinsic variability due to lead placement or body habitus (11). The maximum RWH and TWH for each patient across the recording period are used to identify arrhythmia risk.

Statistical Analyses

Because this is the first analysis of the association of RWH and TWH with sustained
ventricular arrhythmia, cutpoints to define abnormally high levels of these parameters were unknown. We therefore optimized cutpoints for RWH and TWH based 75th percentile in the cardiomyopathy patients without events in the current study and rounded the values to the nearest 10µV. These values were 160 µV for RWH and 80 µV for TWH. We used a 3-dimensional receiver operator characteristics (ROC) curve (12) to obtain the area under the ROC curve for the combined RWH and TWH thresholds. The sensitivity and specificity were 0.74 and 0.83, respectively. To evaluate the association of sustained VT/VF and arrhythmic death or cardiac arrest with these cutpoints, we employed Kaplan-Meier analysis to calculate arrhythmia-free survival and total survival in a multivariate model that controlled for age, sex and LVEF.

Discrete patient characteristics were compared with Fisher’s exact test. Continuous variables were compared using Pearson’s correlation. Significant differences in RWH and TWH levels were analyzed by Student’s t-test. Analysis of variance was used with Tukey test to correct for multiple comparisons (p<0.05). Wilcoxon test was used to compare differences between groups. Parameters were expressed as means ± standard error of the means (SEM).

RESULTS

Baseline Clinical Characteristics

During the enrollment period, 184 consecutive patients were examined, of whom 154 met eligibility criteria for the study. Of these, 34 patients did not have analyzable ECG data due to poor quality or insufficient recordings and were excluded from analysis, leaving a total of 120 patients in the study. Baseline characteristics of the patients were grouped according to the presence (N=70) or absence (N=50) of cardiomyopathy and VT/VF during follow-up (Table 1).
Clinical Outcomes

During the 31-month (mean; range: <1 to 168) follow-up period, 42 (60%) of the 70 cardiomyopathy patients experienced sustained VT/VF (Fig. 2, Table 1); 13 (31%) of these patients with sustained VT/VF experienced arrhythmic death or cardiac arrest. A greater proportion of patients with than without CAD, prior MI, CAD-related cardiomyopathy, recent VT/VF, and positive EP study had sustained VT/VF (Table 1). The arrhythmias were monomorphic or pleomorphic VT (i.e., monomorphic VT with different morphologies) in 31 (74%) patients, polymorphic VT or VF in 4 (10%) patients, and both mono- and pleomorphic VT and polymorphic VT/VF in 7 (17%) patients. Among these 42 cardiomyopathy patients with VT/VF, 36 (86%) had an ICD at enrollment and received appropriate ICD therapies (35 with ICD shocks and 1 with anti-tachycardia pacing only). The remaining 6 (14%) cardiomyopathy patients with arrhythmias did not have ICDs at enrollment but presented with symptomatic sustained monomorphic VT.

All 6 deaths occurred in patients with CAD-related cardiomyopathy who experienced VT/VF during follow-up and all were ascribed to arrhythmic causes. Two patients experienced out-of-hospital SCD and the other 4 died in the hospital after presenting with monomorphic VT storm (Fig. 3). Seven additional cardiomyopathy patients (5 CAD-related, 2 non-CAD-related) had resuscitated VF arrests.

Relationship of Clinical Outcomes to Interlead ECG Morphology Heterogeneity

Representative ECG recordings from cardiomyopathy patients with and without arrhythmia illustrate RWH and TWH as a splay in the depolarization and repolarization waveforms that can readily be visualized in the superimposed ECGs (Fig. 1). Of the 42 cardiomyopathy
patients with VT/VF during follow-up, a majority, 29 (69%), had elevated RWH and/or TWH (Table 1, Fig. 2); likewise, a majority (85%) of the 13 cardiomyopathy patients who died or experienced cardiac arrest had elevated RWH and/or TWH (Fig. 3).

RWH was elevated above the 160-µV cutpoint in 18 (43%) cardiomyopathy patients with VT/VF and in only 6 (21%) event-free cardiomyopathy patients. The group mean RWH level of cardiomyopathy patients with VT/VF (n=42: 163±19 µV) was significantly higher than among the patients without cardiomyopathy (n=50: 62±4 µV, p<0.001) and trended towards a significant elevation over event-free patients with cardiomyopathy (group mean, n=28: 128±17 µV, p=0.067) (Fig. 2, Table 1). TWH was elevated above the 80-µV cutpoint in 20 (48%) of the cardiomyopathy patients with VT/VF and in only 4 (14%) event-free cardiomyopathy patients. The group mean TWH level of cardiomyopathy patients with VT/VF (n=42: 95±11 µV) was higher than among those without cardiomyopathy (group mean, n=50: 20±2 µV, p<0.001) (Fig. 2, Table 1) and was elevated compared to the 4 (14%) event-free cardiomyopathy patients (group mean, n=28: 44±9 µV, p=0.002). Patients with idiopathic VT (RWH 70±11 µV; TWH 23±5 µV; n=15) or SVT (RWH 58±4 µV; TWH 19±2 µV; n=35) but without cardiomyopathy did not exhibit elevated levels of either RWH or TWH (Table 1, Fig. 2).

Among the 13 cardiomyopathy patients who died or were resuscitated, TWH alone (105±24 µV) was elevated above the 80-µV cutpoint and was significantly higher than among cardiomyopathy survivors (group mean, n=57: 67±8 µV, p<0.002) (Fig. 3) and also than among cardiomyopathy patients without VT (group mean, n=28: 44±9 µV, p<0.002) (Table 1). RWH alone did not distinguish among cardiomyopathy patients who died from survivors (164±17 vs. 146±16 µV, p<0.46).
Analysis of the PQ segment with the present method revealed no statistical difference between noise levels between cardiomyopathy patients with VT/VF (n=42: 0.16±0.06 μV), cardiomyopathy patients without VT/VF (n=28: 0.13±0.04 μV, p<0.001), patients without cardiomyopathy but with idiopathic VT (n=15: 0.14±0.06 μV), and patients without cardiomyopathy but with SVT (n=35: 0.16±0.04 μV), 2-way ANOVA (p<0.88). This low level of noise is consistent with the fact that the patients were resting quietly in a supine position and that there was meticulous attention to skin preparation and positioning the electrodes, as is standard practice in the electrophysiology laboratory.

Kaplan-Meier analysis of cardiomyopathy patients (n=70) revealed significant differences in arrhythmia-free survival (p=0.012) as well as total survival (p=0.011) using the combined cutpoint of >160 μV for RWH and/or >80 μV for TWH (Fig. 4, 5). There were no significant differences in age, sex, LVEF, coronary artery disease, prior MI, ICD use, hypertension, diabetes, NYHA class, cardiomyopathy etiology, prior 5-year history of VT or VF, or positive EP study based on these RWH and TWH cutpoints (Table 2). With Kaplan-Meier analysis, RWH or TWH singly did not discriminate in terms of arrhythmia-free survival or survival.

Interlead ECG Heterogeneity Morphology and Etiology of Cardiomyopathy

Among non-CAD related cardiomyopathy patients, RWH (group mean, n=33: 163±5 μV) exceeded the 160-μV cutpoint although it was not statistically greater than among patients with CAD-related cardiomyopathy (group mean, n=37: 133±2 μV, p=0.26). TWH also did not differ among patients with CAD-related compared to non-CAD-related cardiomyopathy (group means: 68±14 vs. 78±9 μV, p=0.56), respectively.
Interlead ECG Morphology Heterogeneity and Intraventricular Conduction

Cardiomyopathy patients with heightened RWH and/or TWH had significantly wider QRS intervals than did those with low RWH and TWH levels (130±5 vs. 113±4 msec, p=0.016) (Table 2), suggesting that intraventricular conduction abnormality might account for elevated interlead ECG morphology heterogeneity in this cohort. However, there was no significant difference in QRS duration comparing patients with and without ventricular arrhythmia (Table 1).

In patients with cardiomyopathy, the presence of either right or left bundle branch block did not appear to affect either RWH (without: 146±16 µV; with: 163±27 µV, p=0.59) or TWH levels (without: 76±10 µV, with: 66±10 µV, p=0.49). There were no differences in RWH or TWH levels comparing patients with left bundle branch block (LBBB) or right bundle branch block (RBBB).

DISCUSSION

This is the first study to provide evidence that interlead depolarization and repolarization morphology heterogeneity is associated with sustained ventricular arrhythmia, appropriate ICD therapies, and arrhythmic death or cardiac arrest among cardiomyopathy patients independent of age, sex, and LVEF (Figs. 2, 3). A majority (69%, 29 of 42) of cardiomyopathy patients who met the primary endpoint exhibited RWH >160 µV and/or TWH >80 µV (Table 1, Fig. 2). Thus, the sensitivity of interlead heterogeneity of ECG morphology was greater than the standard criteria of recent history of VT/VF, which identified arrhythmia risk in 11 patients, or positive EP study, which confirmed risk in 8
patients. Moreover, elevated RWH and TWH based on this combined cutpoint identified 85% (11 of 13) of cardiomyopathy patients who met the secondary endpoint. Elevated TWH alone but not RWH alone separated cardiomyopathy patients who met the secondary endpoint (Fig. 3). Kaplan-Meier analysis demonstrated that heightened levels of RWH and/or TWH in cardiomyopathy patients are significantly associated with increased incidence of sustained VT/VF and arrhythmic death or cardiac arrest (Fig. 4, 5). Moreover, these combined parameters distinguished patients with electrical and/or structural derangements, thus allowing a thorough assessment of the complex interplay of electroanatomic substrates in propensity to ventricular arrhythmias.

Conduction and Repolarization Heterogeneity in Ventricular Arrhythmogenesis

The assessment of both depolarization and repolarization morphology heterogeneity with a single tool affords an important insight into their relative contributions to arrhythmogenesis. Abnormal conduction and repolarization are the hallmarks of some types of arrhythmogenic substrate (13). In the healed post-infarct myocardium, abnormal conduction occurs through an infarct border zone due to altered connectivity of surviving myocytes as they are enveloped by fibrous tissue strands and gap junctional components of intercalated discs undergo remodeling (14). Abnormal conduction through diseased myocardium, whether through gross structural remodeling of scarred myocardium or subcellular ionic or gap junctional remodeling, may manifest electrocardiographically as interlead splay of waveforms. Abnormal repolarization in terms of TWA has been conclusively linked with arrhythmic risk (9). Repolarization heterogeneity interacts with abnormal conduction in electrically and structurally remodeled diseased hearts to result in reentry and wavebreak (15). Thus, ventricular arrhythmias develop from a dynamic interaction of both depolarization and repolarization heterogeneity.
A noninvasive tool that combines the assessment of both parameters during the routine flow of clinical care may offer important opportunities for risk assessment. The present technique of RWH and TWH analysis assesses the intrinsically abnormal electrophysiological heterogeneity that underlies and heralds the onset of TWA (6-8). As it can be monitored from 12-lead ECGs (10), it can potentially be used to track dynamic changes in the electroanatomic substrate to assess arrhythmia risk over time. Our findings validate depolarization and repolarization heterogeneity as useful biological markers of an unstable electrical substrate in patients with cardiomyopathy. Probing RWH and TWH provides additional information about arrhythmic propensity that is not apparent from assessments of global cardiac function and may be more strongly associated with VT/VF than are standard measures such as LVEF, which did not stratify arrhythmia risk in the present study (Table 1).

Comparison with Prior Work

The results of the present study extend prior clinical and experimental work from our laboratory. We previously demonstrated in canines that acute myocardial ischemia induces a large increase in TWH that peaks before the appearance of TWA followed by VF (6,7). This finding underscores the close mechanistic linkage between TWH and TWA, an advanced state of electrical instability resulting from increased interlead morphology heterogeneity and culminating in VF. We subsequently confirmed and extended these findings in a study of patients hospitalized with decompensated heart failure whose ambulatory ECG recordings were analyzed for occurrence of VT (8). High levels of both RWH and TWH preceded the appearance of TWA and subsequently nonsustained VT. In the sizeable 5600-subject Health Survey 2000, which was designed to represent the entire Finnish population, depolarization and repolarization heterogeneity in resting 12-lead ECGs was associated with significantly
enhanced risk for sudden cardiac death (10). The effects of pharmacologic interventions in experimental models have also indicated the suitability of TWH as an indicator of antiarrhythmic efficacy as we (16-18) found that selective inhibition of the cardiac late sodium current abolished the ischemia- or adrenergically induced increase in TWH in parallel with vulnerability to ventricular arrhythmias in porcine hearts.

Relationship to ECG Heterogeneity to Intraventricular Conduction Abnormality

QRS duration was greater in patients with elevated RWH and/or TWH than in those with lower heterogeneity levels (Table 2). This finding is consistent with the fact that RWH reflects conduction abnormalities as do QRS fragmentation (19,20) and signal averaged ECG (21). However, there was no significant difference in QRS duration comparing patients with and without ventricular arrhythmia in this cohort (Table 1).

Study Limitations

This analysis of consecutive patients referred for EP study at a single tertiary care center is limited by small sample size and inherent selection bias or time of study entry in the course of the disease. Despite this fact, the results underscore the strength of the association of elevated RWH and TWH with sustained VT/VF and arrhythmic death or cardiac arrest. The cutpoints employed require validation in larger studies. A single 3-min 12-lead ECG recording during rest was used for analysis of RWH and TWH. Longitudinal analysis is required to assess changes in RWH and TWH over time, as they may fluctuate dynamically. Variabilities in the patients’ autonomic state within the EP laboratory may influence interlead ECG morphology heterogeneity values (22). Nevertheless, we did not observe a significant correlation between heart rate and RWH or TWH levels. Although ICD programming was
not uniform, we found no significant differences in programming among patients with or without appropriate ICD therapies. Moreover, all sustained ventricular arrhythmias were adjudicated to be clinically significant as they resulted in symptoms, hospitalization, or change of therapy, i.e., initiation of antiarrhythmic medications or VT ablation. This analysis is hypothesis generating as larger studies are necessary to determine the extent of effects of cardiomyopathy etiology and intraventricular conduction abnormality on interlead heterogeneity of ECG morphology. In light of recent evidence that respiration has predictive value for total mortality (23), the relationship between ECG heterogeneity and respiration deserves further study.

CONCLUSION

Combined noninvasive assessment of interlead RWH and TWH by second central moment analysis from 3-minute ECGs recorded during rest can distinguish cardiomyopathy patients with potential for sustained ventricular arrhythmia, appropriate ICD therapies, and arrhythmic death or cardiac arrest independent of LVEF and other standard variables.

REFERENCES


LEGENDS:

Fig. 1: Heterogeneity of depolarization and repolarization morphology in representative cardiomyopathy patients with (upper panels) and without ventricular tachycardia (VT) (lower panels). Recordings of precordial leads V4, V5, and V6 are shown in the left panels. Signals were preprocessed, including noise filtering and baseline wander removal. The tracings were then superimposed and heterogeneity was calculated using second central moment analysis (right panels). This process involved determining a computer-generated mean morphology, which is referred to as the “first moment,” or “central axis.” The second central moment, or mean-square deviation, was then determined to quantify the variability or splay about the mean morphology. The maximum square root of the second central moment was calculated to obtain the heterogeneity values in microvolts. The measurements were made on a beat-to-beat basis and the results were averaged for each 15-sec epoch. The values reported below the superimposed complexes are the heterogeneity.
levels. The representative cardiomyopathy patient with VT (upper panel) exhibits greater depolarization and repolarization heterogeneity than the patient without VT (lower panel). See text for details.

Fig. 2: Interlead R-wave heterogeneity (RWH) and T-wave heterogeneity (TWH) levels in the entire study population according to cardiomyopathy (CM) status and arrhythmia incidence (N=120). Patients with CM (N=70) had significantly elevated RWH (p<0.01) and TWH (p<0.01) compared to those without CM (N=50). Moreover, CM patients with ventricular tachycardia (VT) (N=42) had higher TWH levels (p<0.05) but not RWH levels than those without VT/VF (N=28). Dotted line: RWH >160 (top graph) and TWH >80 μV cutpoints (bottom graph).
Fig. 3: Interlead R-wave heterogeneity (RWH) and T-wave heterogeneity (TWH) levels in cardiomyopathy (CM) patients (N=70) comparing those who died to survivors. TWH (p<0.002) but not RWH (p=0.46) was elevated in CM patients who died or were resuscitated (N=13) compared to survivors (N=57). Dotted line: RWH >160 (top graph) and TWH >80 μV cutpoints (bottom graph).
Fig. 4: Three-dimensional receiver operator characteristic (ROC) curve determined that the area under the ROC curve for the combined RWH and TWH thresholds was 0.71.
Fig. 5: Arrhythmia-free survival (upper panel) and total survival (lower panel) in all cardiomyopathy (CM) patients (N=70) according to Kaplan-Meier plots. CM patients with arrhythmic events (N=42) had elevated interlead R-wave morphology heterogeneity (RWH) (>160 µV) and/or T-wave morphology heterogeneity (TWH) (>80 µV) compared to those without events (N=28, p=0.012). CM patients who died (N=6) or were resuscitated (N=7) had elevated RWH (>160 µV) and/or TWH (>80 µV) compared to survivors (N=57, p=0.011).

Table 1. Baseline characteristics of patients
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<th></th>
<th>CM+, VT+ (n=42)</th>
<th>CM+, VT- (n=28)</th>
<th>CM-, Idiopathic VT+ (n=15)</th>
<th>CM-, SVT+ (n=35)</th>
<th>Significance for CM+, VT+ vs. VT- (*p)</th>
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<td>CAD-related (%)</td>
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<td>8 (29)</td>
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<td>Non-CAD related (%)</td>
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<td>20 (71)</td>
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VT/VF in prior 5 years

| Positive EPS (%) | 8/9 (89) | 0/7 (0) | - | - | 0.001 |
| RWH (mean ± SEM) | 163±19 | 128±17 | 70±11 | 58±4 | 0.067 |
| RWH >160 μV (%) | 18 (43) | 6 (21) | 2 (13) | 0 | 0.064 |
| TWH (mean ± SEM) | 95±11 | 44±9 | 23±5 | 19±2 | 0.002 |
| TWH >80 μV (%) | 20 (48) | 4 (14) | 0 | 0 | 0.004 |
| RWH >160 μV and/or TWH >80 μV | 29 (69) | 8 (29) | 2 (13) | 0 | 0.0009 |

Key: CAD = coronary artery disease; CM = cardiomyopathy; DM = diabetes mellitus; EPS = electrophysiologic study; HTN = hypertension; ICD = implantable cardioverter/defibrillator; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; RWH = R-wave heterogeneity; SVT = supraventricular tachycardia; TWH = T-wave heterogeneity; VF = ventricular fibrillation; VT = ventricular tachycardia

Table 2. Baseline characteristics of cardiomyopathy patients with and without elevated interlead ECG morphology heterogeneity
<table>
<thead>
<tr>
<th></th>
<th>RWH &gt;160 µV and/or TWH &gt;80 µV (n=37)</th>
<th>RWH ≤160 µV and TWH ≤80 µV (n=33)</th>
<th>Significance (<em>p</em>)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.3±2.2</td>
<td>62.1±2.5</td>
<td>0.348</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>28 (76)</td>
<td>24 (73)</td>
<td>0.406</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>29±1</td>
<td>30±2</td>
<td>0.67</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>25 (68)</td>
<td>15 (45)</td>
<td>0.241</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>23 (62)</td>
<td>12 (36)</td>
<td>0.152</td>
</tr>
<tr>
<td>ICD (%)</td>
<td>32 (86)</td>
<td>24 (73)</td>
<td>0.381</td>
</tr>
<tr>
<td>HTN (%)</td>
<td>27 (73)</td>
<td>27 (82)</td>
<td>0.22</td>
</tr>
<tr>
<td>DM (%)</td>
<td>8 (22)</td>
<td>11 (33)</td>
<td>0.19</td>
</tr>
<tr>
<td>QRS duration (msec)</td>
<td>130±5</td>
<td>113±4</td>
<td>0.016</td>
</tr>
<tr>
<td>NYHA Class</td>
<td></td>
<td></td>
<td>0.18</td>
</tr>
<tr>
<td>I or II (%)</td>
<td>16 (43)</td>
<td>16 (48)</td>
<td></td>
</tr>
<tr>
<td>III or IV (%)</td>
<td>21 (57)</td>
<td>17 (52)</td>
<td></td>
</tr>
<tr>
<td>Etiology of CM</td>
<td></td>
<td></td>
<td>0.154</td>
</tr>
<tr>
<td>CAD-related (%)</td>
<td>24 (65)</td>
<td>13 (39)</td>
<td></td>
</tr>
<tr>
<td>Non-CAD related (%)</td>
<td>14 (38)</td>
<td>19 (58)</td>
<td></td>
</tr>
<tr>
<td>VT/VF history in prior 5 years (%)</td>
<td>6 (16)</td>
<td>5 (15)</td>
<td>1.00</td>
</tr>
</tbody>
</table>
Positive EPS (N=8/16) 4/4 (100) 4/12 (33) 0.08

Key: Abbreviations as in Table 1.

Technical appendix: Second central moment analysis of spatial heterogeneity of R-wave and T-wave morphology

The following descriptions are based in part on the methodologic details provided in the original publication of this method in *Journal of Applied Physiology* (1), a study conducted by two of the current authors. As this publication dealt only with T-wave heterogeneity (TWH), additional test data are provided for R-wave heterogeneity (RWH), as it is relevant to the current study.

The square root of the second central moment of simultaneous T waves was computed to quantify the variability about the mean morphology (Figs. 1 and 2) (1). Specifically, R waves are identified and an average waveform is computed on a point-by-point basis

\[
e(t) = \frac{1}{4} \sum_{i=1}^{4} e_i(t)
\]

where \(e_i(t)\) is the ECG amplitude as a function of time \(t\) for electrode \(E_i (i = 1 \ldots 4)\). Then, the simultaneous waveforms are superimposed and the second central moment \(\mu_2(t)\) of the T wave is calculated by taking the mean-square deviation, \(\mu_2(t)\), of the waveforms about the average waveform

\[
\mu_2(t) = \frac{1}{4} \sum_{i=1}^{4} [e_i(t) - e(t)]^2
\]
TWH is then calculated as the maximum square root of the second central moment occurring within the J-T interval on a beat-to-beat basis:

$$\text{TWH} = \max_t \sqrt{\mu_2(t)}$$

The function MAX of $t$ indicates taking the maximum value of the square root function for all values of $t$ between 60 and 29 ms after the R-wave. The results are averaged for each 15-sec interval.

The accuracy of the algorithm was examined by measuring TWH in simulated ECGs generated by a C++ program, having P waves, R waves, T waves, and ST segments approximated by geometric shapes whose relative timing and amplitude were similar to surface ECGs. The resulting TWH readings were compared with input TWH of 0 to 800 μV that was centered during the first half of the T wave, the period in the cardiac cycle when enhanced heterogeneity of repolarization is known to occur (3). Detection of TWH of this level has been sufficient for our experimental studies. We also assessed the algorithm’s capacity to measure TWH in simulated ECGs with ST segment deviation, prominent U waves, and T-wave inflections, which are common in routine clinical and experimental ECGs and which confound current approaches to measuring spatial heterogeneity of repolarization.

The test data are provided in Figures 3-6 of the methodology description in Journal of Applied Physiology (1).

R-wave heterogeneity has undergone similar testing. The main difference is that the interval tested encompassed the beginning of the Q wave to the end of the S wave rather than the JT interval, as was illustrated in Fig. 1. Results of the basic signal testing are shown in Fig. 3.
REFERENCES


LEGENDS

Fig. 1: Flow chart of the second central moment calculation of T-wave heterogeneity (TWH). ECGs were simultaneously obtained from all 4 electrodes of a plaque situated in the anticipated zone of ischemia during a representative experiment in which coronary artery occlusion subsequently resulted in ventricular fibrillation (VF). ECGs were filtered to reduce high-frequency noise and to remove baseline wander. Ventricular and supraventricular premature beats as well as beats with a high noise level were removed. For each electrode, the isoelectric level was made uniform, and the waveforms of successive beats were superimposed (Bₙ, Bₙ₊₁, Bₙ₊₂, etc.) Second central moment is a square function, as it is the computation of area around a central axis. The square root of the second central moment of the T waves (from the J point to the end of the T wave) was computed from the superimposed waveforms to measure deviation among the T waves. The maximum square root of the
second central moment was identified for each beat. An average TWH value was computed for each 15-sec interval.

Fig. 2. Superimposition of 4 simultaneous simulated ECG waveforms (A–D) illustrates heterogeneity of T-wave morphology, the parameter measured by second central moment analysis. ECGs A–D were simulated ECGs of identical morphology with the exception of the amplitude of the parabolic-shaped T wave. The peak T-wave amplitude of ECGs A–D were 500-2ΔV, 500-ΔV, 500+ΔV, and 500+2ΔV (in μV), where ΔV ranged from 10 to 500 μV depending on the desired amount of simulated TWH. Theoretical TWH, without noise, can be calculated as ΔV multiplied by the square root of 2.5.

Fig. 3: Calibration curve demonstrating a linear relationship between the R-wave heterogeneity (RWH) value estimated by second central moment analysis and the RWH input signal in simulated ECG waveforms. RWH was elevated in 50 equal intervals from 0 to 800 μV. Regression analysis yielded a correlation of $r^2 = 0.999$, with $p<0.001$.

FIGURES

Fig. 1:
Fig. 2:

**T-Wave Heterogeneity Analysis**

- E1
- E2
- E3
- E4

**Noise Reduction, Baseline Wander Removal**

- Removal of Isoelectric Level from ECG E1,E2,E3,E4 superimposing the waveforms

- Compute Heterogeneity of superimposed ECG waveforms

- T-Wave Heterogeneity (μV)

- JT Interval

- Time

- Compute Maximum for Each Beat between J-Point and End of T-Wave

- Compute Average of Maximum Values for each 15 second interval

**T-Wave Heterogeneity Values in microvolts**

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**Simulated ECG Waveforms with Known Heterogeneity Values**

A  
B  
C  
D  

**Superimposition of ECG Waveforms**

**T-Wave Morphology Heterogeneity Algorithm**

**Measured Heterogeneity Values**
Fig. 3: