Prediction of sudden cardiac death with automated high-throughput analysis of heterogeneity in standard resting 12-lead electrocardiograms

Tuomas V. Kenttä, PhD,[*†] Bruce D. Nearing, PhD,[†‡] Kimmo Porthan, MD, PhD,[§] Jani T. Tikkanen, MD, PhD,[*‖] Matti Viitasalo, MD, PhD,[§] Markku S. Nieminen, MD, PhD,[§] Veikko Salomaa, MD, PhD,[¶] Lasse Oikarinen, MD, PhD,[§] Antti Jula, MD, PhD,[¶] Kimmo Kontula, MD, PhD,[#] Chris Newton-Cheh, PhD,[**††] Heikki V. Huikuri, MD, PhD,[*] Richard L. Verrier, PhD, FHRS[†‡]

From the [*]Medical Research Center Oulu, University of Oulu and University Hospital of Oulu, Oulu, Finland, [†]Beth Israel Deaconess Medical Center, Boston, Massachusetts, [‡]Harvard Medical School, Boston, Massachusetts, [§]Division of Cardiology, Heart and Lung Center, Helsinki University Central Hospital, Helsinki, Finland, [‖]Emergency Department, Haartman Hospital, Helsinki, Finland, [¶]National Institute for Health and Welfare, Helsinki, Finland, [#]Department of Medicine, University of Helsinki, Helsinki, Finland, [**]Cardiovascular Research Center and Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts, and [††]Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts.

BACKGROUND Heterogeneity of depolarization and repolarization underlies the development of lethal arrhythmias.

OBJECTIVE We investigated whether quantification of spatial depolarization and repolarization heterogeneity identifies individuals at risk for sudden cardiac death (SCD).

METHODS Spatial R-, J-, and T-wave heterogeneity (RWH, JWH, and TWH, respectively) was analyzed using automated second central moment analysis of standard digital 12-lead electrocardiograms in 5618 adults (2588, 46% men; mean ± SEM age 50.9 ± 0.2 years), who took part in the epidemiological Health 2000 Survey as representative of the entire Finnish adult population.

RESULTS During the follow-up period of 7.7 ± 0.2 years, a total of 72 SCDs occurred (1.3%), with an average yearly incidence rate of 0.17% per year. Increased RWH, JWH, and TWH in left precordial leads (V_4–V_6) were univariately associated with SCD ($P < .001$ for each). When adjusted with standard clinical risk markers, JWH and TWH remained independent predictors of SCD. Increased TWH ($\geq$102 μV) was associated with a 1.7-fold adjusted relative risk for SCD (95% confidence interval [CI] 1.0–2.9; $P = .048$) and increased JWH ($\geq$123 μV) with a 2.0-fold adjusted relative risk for SCD (95% CI 1.2–3.3; $P = .006$). When both TWH and JWH were above the threshold, the adjusted relative risk for SCD was 2.9-fold (95% CI 1.5–5.7; $P = .002$). When RWH ($\geq$470 μV), JWH, and TWH were all above the threshold, the adjusted relative risk for SCD was 3.2-fold (95% CI 1.4–7.1; $P = .009$).

CONCLUSION Second central moment analysis of standard resting 12-lead electrocardiographic morphology provides an ultrarapid means for the automated measurement of spatial RWH, JWH, and TWH, enabling analysis of high subject volumes and screening for SCD risk in the general population.

KEYWORDS Sudden cardiac death; Ventricular arrhythmias; Depolarization; Repolarization; Electrocardiogram; Heterogeneity

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Introduction

Noninvasive identification of individuals at risk for sudden cardiac death (SCD) remains a major clinical challenge, especially in the general population, as the majority of SCDs occurs in subjects with low-to-intermediate risk and in individuals without known risk factors.[1]

Recently, significant attention has been paid to the measurement of ventricular repolarization heterogeneity, which is associated with ventricular tachycardia (VT) and ventricular fibrillation (VF), because the steep electrical

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gradients reflected in this metric set the stage for unidirectional block, reentry, and wavebreak.[2,3] Conversely, interventions that reduce heterogeneity interrupt this cascade of events and prevent malignant arrhythmias. An accurate assessment of risk for SCD from standard 12-lead electrocardiograms (ECGs) would represent a significant advance, as this platform is widely used and well-established. The advent of digital ECG recordings and increased computational power has enabled more complex analyses of ECG morphology. Some of these methods rely on axis transformations,[4] decompositions,[5] and other approaches that are often cumbersome and lack defined mechanistic bases. Therefore, a need remains for a method that could be easily and rapidly implemented, has a sound mechanistic basis, and could be used in guiding therapy.

A technique for quantifying interlead depolarization and repolarization heterogeneity was developed called second central moment analysis,[6,7] which uses a principle drawn from Newtonian mechanics. It measures the simultaneous dissimilarities (i.e., interlead heterogeneity) across ECG leads. This method has been shown in experimental[8–10] as well as clinical[11] studies to track arrhythmia vulnerability and effective antiarrhythmic therapy.[9,10] However, its utility in the prediction of SCD has not been evaluated.

The goal of this study was to quantify depolarization and repolarization heterogeneity in a general population database to determine whether it would be able to discriminate individuals at risk for SCD.

Methods

Study population

The participants in this study were drawn from the Health 2000 Survey (http://www.terveys2000.fi/indexe.html), which is a cross-sectional, general population–based epidemiological survey conducted in Finland between 2000 and 2001.[12] The study enrolled a sample of 8028 Finnish adults aged ≥ 30 and < 80 years representative of the entire Finnish adult population. After baseline participant interviews, health examinations, and exclusion of subjects with preexcitation syndrome, complete bundle branch block, paced rhythm, atrial fibrillation or flutter, low-quality ECG, and use of QT-prolonging medication or digoxin, a total of 5618 eligible participants remained in the cohort. Institutional ethics committees of the Helsinki and Uusimaa hospital districts approved the study, which was performed according to the Declaration of Helsinki. Written informed consent was obtained from all subjects.

ECG

Standard 12-lead ECGs were recorded with the Marquette MAC 5000 electrocardiograph (GE Marquette Medical Systems, Milwaukee, WI). Representative median beats for each of the 12 leads were produced from the 10-second ECG strip with QT Guard 1.3 (GE Marquette Medical Systems). Subsequently, fully automated second central moment analysis[6,7] was performed on the median beats to determine spatial R-, J-, and T-wave heterogeneity (RWH, JWH, and TWH, respectively) in left precordial leads (V_4–V_6).

Second central moment is a concept from Newtonian mechanics that refers to a measure of splay of waveforms around the first moment, which in this case is the average waveform of QRS complex, J wave, or T wave. Thus, heterogeneity is measured throughout the entire waveform. The entire database was analyzed within 15 minutes, as automated ultrarapid ECG heterogeneity analysis required < 1 second per subject. ECG morphology was retained for the clinical interpretation of the analyzed waveforms.

Follow-up and adjudication of SCD

Follow-up started at the study baseline and lasted until January 1, 2009. Adjudication of the cause of death was based on the national registers on drug reimbursement, hospital admission and discharge, and causes of deaths. The validity of Finnish national registries has been shown to be high.[13] Registers were analyzed independently by 2 physicians, who classified deaths as probable SCD, possible SCD, unlikely SCD, and unknown cause of death. In cases of disagreement, the final decision was made by consensus of 4 physicians including 2 independent physicians. Resuscitated cardiac arrests were included in the definition of SCD. Out-of-hospital deaths and deaths within 10 days of hospitalization were considered eligible for the adjudication of SCD. Probable SCDs included all deaths with a cardiac cause as the immediate or underlying cause of death and without any known cause of death other than arrhythmia. Possible SCDs included deaths with a noncardiac cause as the immediate or underlying cause of death when cardiac disease was present and could reasonably have contributed to arrhythmia. In the present study, probable and possible SCDs were pooled in the analyses and all other deaths were considered as censored observations. Autopsies were performed in 48 (67%) SCDs.

Statistics

Comparisons between participants with and without events were made using the nonparametric U test for unequally distributed data and independent samples and using the t test for normally distributed data. Categorical variables were compared using the Fisher exact test. The univariate and multivariate hazard ratios for all end points were estimated using the Cox proportional hazards model. All continuous risk variables were dichotomized according to their optimal cut points obtained from the receiver operating characteristic curves for risk analysis, with sensitivity of at least 20% and cutoff values above the mean of survivors. In the multivariate Cox regression analysis, a clinical model was constructed out of the clinical markers using stepwise backward regression analysis. The multivariate model included age, sex, body mass index, systolic blood pressure, total cholesterol/high-density lipoprotein ratio, heart rate, ECG signs of left ventricular hypertrophy, QRS duration, arterial hypertension, current smoking, diabetes, coronary artery disease, and previous myocardial infarction. In order to allow

comparisons among heterogeneity variables, unadjusted and adjusted hazard ratios were calculated per increment of 1 SD. The proportional hazard assumption was verified for each risk marker by plotting Schoenfeld residuals against survival time transformed into natural logarithms. All the covariates fulfilled the proportionality assumption. Kaplan-Meier survival curves were developed with groups stratified according to the optimal cut points, and groups were compared using the log-rank test. Improvement in model discrimination for SCD with the inclusion of new heterogeneity markers was assessed using the C index and continuous net reclassification improvement.[14] Analyses were performed using SPSS version 21 (IBM SPSS Statistics, Armonk, NY) and R Statistics (3.1.2, The R Foundation for Statistical Computing, Vienna, Austria). All tests were 2-sided, and $P \leq .05$ was considered statistically significant.

Results

A total of 307 subjects (5.4%) died during the follow-up period of 7.7 ± 0.2 years. Of these 307 deaths, 94 (1.7%) were classified as cardiac deaths including 72 (1.3%) SCDs. SCDs occurred with an average incidence rate of 0.17% per year. Clinical characteristics and depolarization/repolarization heterogeneities are presented in Table 1 with comparisons among different end points and survivors.

Univariate predictors of SCD

Increased RWH, JWH, and TWH were univariately associated with SCD ($P < .001$ for each) as well as all-cause mortality ($P < .001$ for each) and cardiac death ($P < .001$ for each) (Tables 1 and 2 and Figure 1). Figure 2 illustrates representative ECGs recorded from an SCD case, who exhibited significant heterogeneity in T-wave morphology, and a survivor, in whom T waves were more uniform across the leads.

Multivariate assessment of risk for SCD

Tables 2 and 3 present unadjusted and adjusted hazard ratios and their 95% confidence intervals (CIs) for optimally dichotomized depolarization/repolarization parameters and for increment of 1 SD in these parameters, respectively. After adjustments with clinical covariates, both JWH and TWH but not RWH remained independent predictors of SCD. TWH ≥102 μV was associated with a 1.7-fold adjusted relative risk for SCD (95% CI 1.0–2.9; $P < .048$). JWH ≥123 μV was associated with a 2.0-fold adjusted relative risk for SCD (95% CI 1.2–3.3; $P = .006$). When both JWH and TWH were above the threshold, the adjusted relative risk for SCD was 2.9-fold (95% CI 1.5–5.7; $P = .002$) in contrast to subjects without JWH or TWH abnormalities. When RWH (≥470 μV), JWH, and TWH were all above the threshold, the adjusted relative risk for SCD was 3.2-fold (95% CI 1.4–7.1; $P = .009$). Only JWH and TWH remained predictive of all-cause mortality and cardiac death after adjustments with clinical covariates.

Associations with clinical risk markers

Increased RWH, JWH, and TWH were associated with male sex ($P < .001$ for each), ECG signs of left ventricular hypertrophy (Sokolow-Lyon [>3.5 mV] and/or Cornell voltage [women, >2.0 mV; men, >2.8 mV]) ($P < .001$ for each), and previous myocardial infarction ($P < .001$ for each). Similarly, increased RWH and JWH were associated with arterial hypertension ($P < .001$ for both), coronary artery disease ($P < .001$ for both), and diabetes ($P < .001$ and $P = .044$, respectively), whereas increased TWH was associated with smoking ($P < .001$). Both RWH and JWH had weak positive correlations with systolic blood pressure ($P < .001$ for both) and QRS duration ($P < .001$ for both). Increased heterogeneity in left precordial R and T waves was associated with early repolarization. RWH was increased in subjects with inferior (n = 64 (1%): 422.3 ± 20.1 μV vs

Table 1 Characteristics of the study population

Variable	Alive (n = 5311, 94.5%)	Dead (n = 307, 5.4%)	Cardiac death (n = 94, 1.7%)	SCD (n = 72, 1.3%)
Age (y)	50.18 ± 0.17	63.58 ± 0.67‡	65.7 ± 11.1‡	62.90 ± 1.25‡
Body mass index (kg/m^2)	26.83 ± 0.06	27.64 ± 0.28†	27.08 ± 0.43	27.07 ± 0.49
Systolic blood pressure (mm Hg)	132.59 ± 0.27	143.47 ± 1.29‡	146.55 ± 2.47‡	145.86 ± 2.94‡
Total cholesterol/HDL ratio	4.76 ± 0.02	5.21 ± 0.11‡	5.38 ± 0.19‡	5.56 ± 0.21‡
Heart rate (beats/min)	62.92 ± 0.14	66.70 ± 0.73‡	66.40 ± 1.40†	67.47 ± 1.65†
QRS duration (ms)	92.95 ± 0.13	93.82 ± 0.59	95.87 ± 1.26†	96.00 ± 1.44†
Sex: male	2398 (45)	190 (62)‡	69 (73)‡	58 (81)‡
Smoking	1175 (22)	112 (37)‡	38 (40)‡	35 (49)‡
LVH (ECG)	742 (14)	63 (21)†	25 (27)‡	18 (25)*
Hypertension	2307 (44)	215 (70)‡	73 (78)‡	57 (79)‡
Diabetes	244 (5)	43 (14)‡	13 (14)‡	7 (10)*
Coronary artery disease	233 (4)	61 (20)‡	27 (29)‡	19 (26)‡
Previous myocardial infarction	78 (2)	32 (10)‡	16 (17)‡	11 (15)‡
R-wave heterogeneity (μV)	365.99 ± 2.51	451.63 ± 14.22‡	480.93 ± 26.45‡	481.26 ± 31.55‡
J-point heterogeneity (μV)	117.50 ± 1.33	160.16 ± 7.65‡	174.56 ± 14.94‡	184.74 ± 17.49‡
T-wave heterogeneity (μV)	94.21 ± 0.88	118.90 ± 4.49‡	137.63 ± 8.93‡	139.99 ± 10.78‡

Values are presented as mean ± SEM or as n (%). Significance levels compare survivors and subjects who died during the follow-up period: *$p \leq .05$; †$p < .01$; ‡$p < .001$.
ECG = electrocardiogram; HDL = high-density lipoprotein; LVH = left ventricular hypertrophy; SCD = sudden cardiac death.

Table 2 Unadjusted and adjusted hazard ratios for optimal cut points of the left precordial depolarization and repolarization heterogeneity variables

		Hazard ratio (95% CI)		
End point in 5618 subjects	Events per subjects at risk (%)	Unadjusted	Age- and sex-adjusted	Multivariate adjusted
All cause mortality (n = 307, 5.4%)				
RWH (≥454 μV)	121/1470 (8%)	1.9 (1.5–2.4)‡	1.2 (0.9–1.6)NS	1.2 (0.9–1.5)NS
JWH (≥154 μV)	135/1552 (9%)	2.2 (1.7–2.7)‡	1.5 (1.2–1.9)‡	1.5 (1.2–1.9)‡
TWH (≥105 μV)	150/1931 (8%)	1.9 (1.5–2.4)‡	1.6 (1.3–2.0)‡	1.6 (1.2–2.0)‡
JWH + TWH	61/554 (11%)	3.3 (2.4–4.4)‡	2.2 (1.6–3.0)‡	2.1 (1.5–2.9)‡
RWH + JWH + TWH	62/521 (12%)	4.0 (2.8–5.7)‡	2.5 (1.7–3.5)‡	2.3 (1.6–3.3)‡
Cardiac death (n = 94, 1.7%)				
RWH (≥470 μV)	41/1337 (3%)	2.6 (1.7–3.8)‡	1.6 (1.1–2.5)*	1.3 (0.8–2.0)NS
JWH (≥123 μV)	56/2002 (3%)	2.5 (1.7–3.8)‡	1.7 (1.1–2.6)*	1.6 (1.1–2.5)*
TWH (≥117 μV)	51/1537 (3%)	3.0 (2.0–4.5)‡	2.3 (1.5–3.5)‡	2.1 (1.3–3.2)†
JWH + TWH	33/747 (4%)	5.9 (3.4–10.3)‡	3.4 (1.9–6.0)‡	2.9 (1.6–5.2)‡
RWH + JWH + TWH	24/493 (5%)	7.5 (3.9–14.3)‡	3.0 (1.5–5.8)‡	3.5 (1.7–7.0)‡
Sudden cardiac death (n = 72, 1.3%)				
RWH (≥470 μV)	31/1337 (2%)	2.5 (1.6–4.0)‡	1.5 (0.9–2.5)NS	1.2 (0.8–2.0)NS
JWH (≥123 μV)	47/1993 (2%)	3.2 (2.0–5.3)‡	2.0 (1.2–3.3)†	2.0 (1.2–3.3)†
TWH (≥102 μV)	44/1924 (2%)	2.8 (1.8–4.5)‡	1.8 (1.1–3.0)*	1.7 (1.0–2.9)*
JWH + TWH	32/901 (4%)	6.5 (3.4–12.4)‡	3.0 (1.6–5.9)†	2.9 (1.5–5.7)†
RWH + JWH + TWH	19/493 (4%)	9.0 (4.2–19.3)‡	3.5 (1.6–7.6)†	3.2 (1.4–7.1)†

Multivariate stepwise backward model included age, sex, body mass index, systolic blood pressure, total cholesterol/high-density lipoprotein ratio, heart rate, electrocardiographic signs of left ventricular hypertrophy, QRS duration, arterial hypertension, current smoking, diabetes, coronary artery disease, and previous myocardial infarction.

CI = confidence interval; JWH = J-wave heterogeneity; RWH = R-wave heterogeneity; TWH = T-wave heterogeneity.

Significance levels: NS = not significant, $p > .05$; *$p \leq .05$; †$p < .01$; ‡$p < .001$.

370.0 ± 2.5 μV, $P = .028$); and lateral (n = 140 (2%): 406.1 ± 16.8 μV vs 369.8 ± 2.5 μV, $P = .024$) early repolarization. Similarly, TWH was increased in subjects with inferior (159.2 ± 10.3 μV vs 94.8 ± 0.9 μV, $P < .001$) and lateral (157.5 ± 7.0 μV vs 94.0 ± 0.9 μV, $P < .001$) early repolarization. Decreased JWH values were associated with lateral early repolarization (87.3 ± 7.6 μV vs 120.7 ± 1.3 μV, $P < .001$).

Kaplan-Meier curves

Kaplan-Meier curves (Figure 3) indicated that each of the heterogeneity measures predicted SCD ($P < .001$ for each). The curves first began to diverge significantly at 16 months. Areas under the receiver operating characteristic curves for SCD were 0.637, 0.649, and 0.666 for RWH, JWH, and TWH, respectively. There was a marginal improvement in model discrimination (C index) when any of the new heterogeneity markers or a combination of them all was entered into the model (Table 4). Similarly, continuous net reclassification improvement improved statistically significantly, indicating that overall individual risks were adjusted in the right direction within the SCD and non-SCD groups with the inclusion of the new heterogeneity markers.

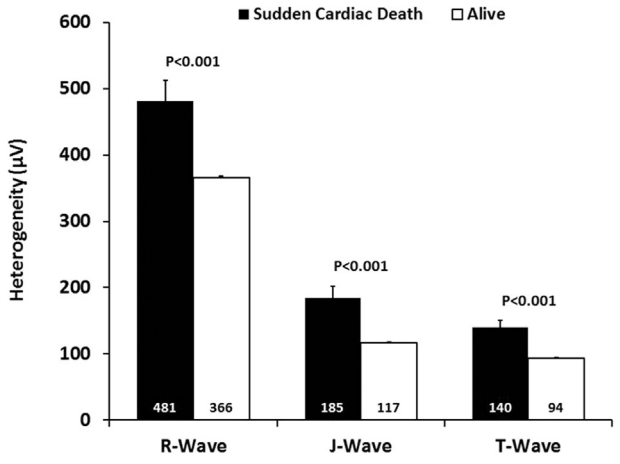

Figure 1 R-wave heterogeneity, J-wave heterogeneity, and T-wave heterogeneity in left precordial leads among sudden cardiac death cases and survivors. Values are presented as mean ± SEM.

Discussion

This is the first study to demonstrate that increased spatial depolarization and repolarization heterogeneity, a fundamental property linked to arrhythmogenesis, assessed from resting 12-lead ECGs using second central moment analysis is able to stratify risk for SCD in a general population. The computer processing for the entire database required ~15 minutes, as ECG heterogeneity analysis was performed in <1 second per subject. The high-throughput capacity of the algorithms offers a distinct advantage over many contemporary methods for ECG-based risk assessment. ECG heterogeneity can be visualized by superimposition of waveforms (Figure 2), which are retained for clinical interpretation.

Repolarization abnormalities in 12-lead ECG and SCD

The predictive capacity of several standard 12-lead resting ECG indices for cardiac events and SCD has been reported. Although

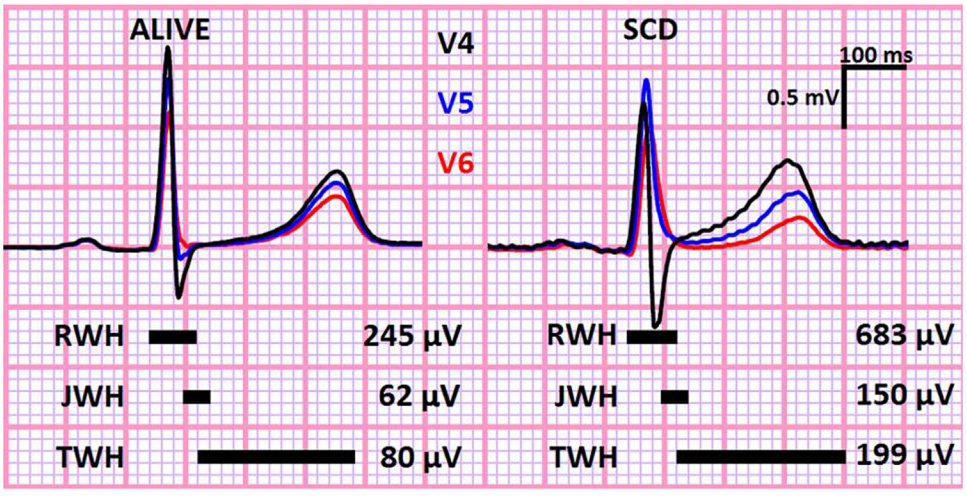

Figure 2 Superimposed left precordial lead ECGs (V_4–V_6) recorded in a survivor (left) and in a subject who suffered sudden cardiac death (SCD) (right) during the follow-up period illustrate R-wave heterogeneity (RWH), J-wave heterogeneity (JWH), and T-wave heterogeneity (TWH). Black horizontal bars indicate the periods when RWH, JWH, and TWH were measured.

Table 3 Unadjusted and adjusted hazard ratios for left precordial depolarization and repolarization heterogeneities per increment of 1 SD

		Hazard ratio (95% CI) per increment of 1 SD		
End point	ECG parameter	Unadjusted	Age- and sex-adjusted	Multivariate adjusted
All cause mortality	R-wave heterogeneity	1.4 (1.3–1.5)‡	1.2 (1.1–1.3)‡	1.2 (1.1–1.3)‡
	J-wave heterogeneity	1.4 (1.3–1.6)‡	1.1 (1.0–1.3)*	1.2 (1.0–1.3)†
	T-wave heterogeneity	1.4 (1.3–1.6)‡	1.2 (1.1–1.4)‡	1.2 (1.1–1.4)‡
Cardiac death	R-wave heterogeneity	1.5 (1.3–1.7)‡	1.2 (1.0–1.4)*	1.1 (0.9–1.3)NS
	J-wave heterogeneity	1.6 (1.3–2.0)‡	1.2 (1.0–1.4)NS	1.2 (1.0–1.4)NS
	T-wave heterogeneity	1.8 (1.5–2.2)‡	1.5 (1.2–1.8)‡	1.4 (1.2–1.8)‡
Sudden cardiac death	R-wave heterogeneity	1.5 (1.3–1.7)‡	1.2 (1.0–1.4)*	1.1 (0.9–1.4)NS
	J-wave heterogeneity	1.8 (1.4–2.3)‡	1.3 (1.1–1.6)*	1.3 (1.0–1.6)*
	T-wave heterogeneity	1.9 (1.5–2.4)‡	1.4 (1.1–1.8)†	1.4 (1.1–1.8)†

Multivariate model included age, sex, body mass index, systolic blood pressure, total cholesterol/high-density lipoprotein ratio, heart rate, electrocardiographic signs of left ventricular hypertrophy, QRS duration, arterial hypertension, current smoking, diabetes, coronary artery disease, and previous myocardial infarction.

CI = confidence interval, SD = standard deviation.

Significance levels: NS = not significant ($p > .05$); *$p \leq .05$; †$p < .01$; ‡$p < .001$.

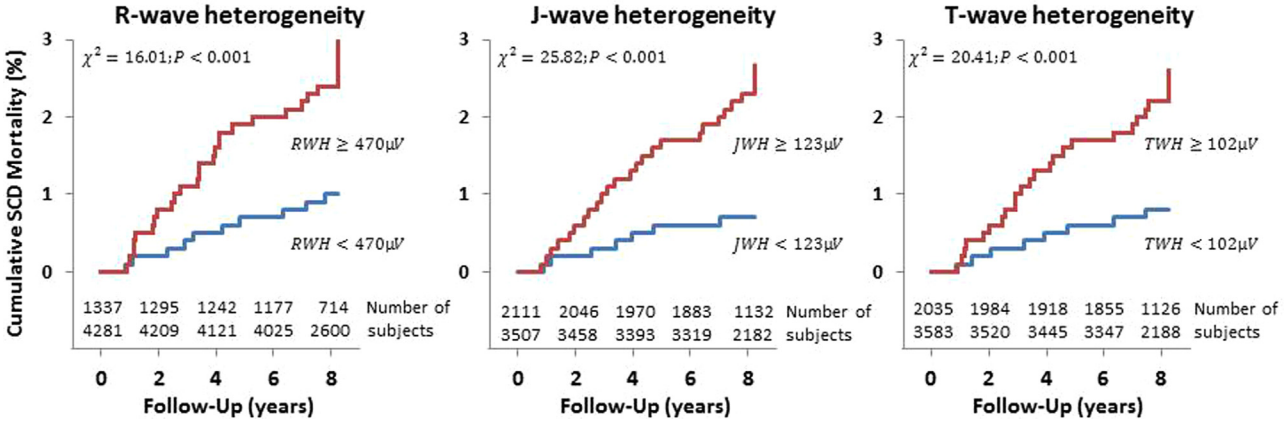

Figure 3 Kaplan-Meier curves of R-wave, J-wave, and T-wave heterogeneity for sudden cardiac death (SCD) with numbers of SCD events.

Table 4 Model discrimination improvement (C index) and net reclassification improvement with the inclusion of novel ECG markers in the clinical model

Model(s)	C index	Continuous NRI (%)
Clinical Model (reference)	0.882 (0.847–0.917)	—
+ RWH (≥470 μV)	0.883 (0.849–0.918)	39.0 (16.0–62.0)‡
+ JWH (≥123 μV)	0.887 (0.853–0.921)	56.1 (34.0–78.3)‡
+ TWH (≥102 μV)	0.884 (0.848–0.920)	50.4 (27.8–73.1)‡
+ RWH/JWH/TWH	0.889 (0.855–0.923)	55.2 (32.7–77.7)‡

ECG = electrocardiographic; JWH = J-wave heterogeneity; NRI = net reclassification improvement; RWH = R-wave heterogeneity; TWH = T-wave heterogeneity.

Significance level: ‡$p < .001$.

prolonged QT interval duration has been associated with an increased risk for cardiovascular events in large general population samples,[15–17] conflicting results have been published,[18,19] first and most notable of which was the Framingham Study.[19] The use of QT interval measurement is further clouded by suboptimal heart rate correction formulas.[15,20]

Two decades ago, interlead variability of QT interval duration, that is, QT dispersion (QTd), was proposed for the prediction of malignant ventricular arrhythmias,[21] as it measured regional differences in repolarization.[15] Although the utility of QTd for risk stratification was verified in several studies,[22–24] many investigators reported conflicting results in similar patient populations[25,26] and others questioned the reliable measurement of this index.[27–29]

T-peak to T-end (TpTe) interval duration was proposed as a means to assess transmural repolarization heterogeneity of the left ventricle and, therefore, susceptibility to ventricular arrhythmias and SCD. Prolonged TpTe interval was associated with an increased risk for mortality in high-risk patients and with SCD in the Oregon Sudden Unexpected Death Study[30] but was not univariately associated with SCD in the Health 2000 Survey.[17]

Spatial repolarization morphology indices have shown predictive capacities in several studies, often outperforming scalar measures of repolarization, such as QT interval, QTd, and TpTe measurements.[5,17,31] Principal component analysis ratio characterizes T-wave complexity and was an independent predictor of cardiovascular mortality in a prospective community-based study that enrolled native Americans.[5] However, in the Health 2000 Survey, it did not predict SCD after adjustments with clinical risk markers,[17] although other T-wave morphology parameters independently predicted SCD, including T-wave morphology dispersion, total cosine R-to-T, and T-wave residuum.

Depolarization abnormalities in 12-lead ECG and SCD

Analysis of late ventricular potentials by signal-averaged electrocardiography indicates a substrate for microreentry in patients with myocardial infarction and in those with known coronary artery disease, cardiomyopathy, or unexplained syncope, factors in lethal ventricular tachyarrhythmias.[32] Signal-averaged electrocardiography analysis requires a specialized recording protocol to assess derangements in the QRS complex. Prolonged QRS duration may reflect intraventricular conduction deficits or the presence of cardiac hypertrophy[32] but does not characterize deviations in morphology.

Present study

We observed a significant association between increased spatial depolarization and repolarization heterogeneity in left precordial leads, measured using the second central moment technique, and SCD.

The arrhythmogenic nature of TWH has been previously demonstrated in experimental studies,[6,8–10] as TWH progressively increased during coronary artery occlusion in animals vulnerable to myocardial ischemia–induced VF, but not in those without VF. This crescendo in TWH levels preceded the appearance of T-wave alternans (TWA), a known risk factor for SCD.[33] With increasing levels of heterogeneity, TWA then evolved to more complex forms and finally culminated in VF, demonstrating that increased heterogeneity of repolarization underlies TWA and increases risk for ischemia-induced VF. Later, Nearing et al[11] showed that both RWH and TWH predicted impending VT in ambulatory ECG recordings of patients hospitalized with decompensated heart failure. Compared with baseline levels, both RWH and TWH showed a marked increase in 30–45 minutes before the onset of VT. In experimental studies, Zhao et al[8] determined that TWH indicates the arrhythmogenic influence of impaired calcium handling and the antiarrhythmic effects of intrapericardial nitroglycerin administration. Verrier et al[9] and Bonatti et al[10] demonstrated that TWH tracks antiarrhythmic effectiveness of late sodium current inhibition, as both ranolazine and the experimental late cardiac sodium current inhibitor GS-458967 suppressed TWH in parallel with vulnerability to ischemia-induced ventricular arrhythmias in a porcine model.

Increased JWH in left precordial leads showed a strong association with SCD, indicating significant disarray at the junction of depolarization and repolarization phases. Previously, patients with evidence of early repolarization in inferior and left precordial leads have been observed to have increased risk for cardiac death and SCD.[34,35] In the present study, subjects with early repolarization showed significantly higher lateral TWH values, indicating higher risk for SCD and thus concurring with the previous studies that reported higher incidence of SCD in subjects with early repolarization. However, subjects with lateral early repolarization had paradoxically lower JWH values than did subjects without signs of lateral early repolarization. This finding might be in part due to the predominant early repolarization morphology across the lateral leads, which serves as an anchor and produces similar ECGs across the leads around the terminal part of the QRS complex and thus leads to decreased JWH values.

Measurement of repolarization heterogeneity using second central moment analysis circumvents the limitations that hinder the accurate measurement of ventricular repolarization abnormalities in conventional scalar measures, such as protracted T-wave offsets, inflections in waveforms, ST-segment changes, and presence of U waves.[6] Calculation of variance in the morphology of neighboring leads is less complex than that of other T-wave morphology descriptors, which require axis transformations[4] and various decompositions.[5] Availability of superimposed median beats allows physicians to verify automated repolarization heterogeneity output and to interpret waveforms. The strong association of repolarization heterogeneity with SCD and the facts that its measurement is robust and fully automated support its utility as a screening tool.

Study limitations

Probable (n = 52) and possible (n = 20) SCDs were pooled into 1 SCD category, which may cause some inaccuracies in the statistical outcome. In addition, because of the limited access to hospital records, survivors of cardiac arrest could not be included. Left ventricular ejection fraction, which is currently one of the most widely used clinical parameters in the prediction of SCD, was not measured in this study, was assumed typically to be preserved, and thus would not be expected to contribute to risk stratification in this population. As the analyses were performed on a 10-second ECG recording, fluctuations in subjects' autonomic tone could have affected the measurement. It remains to be determined whether long-term monitoring of heterogeneity using ambulatory ECGs or exercise stress testing can provide more accurate information on the propensity for SCD than does a brief analysis using a resting ECG. This possibility could be tested, as the methodology is also suitable for use on these platforms.[11]

Conclusion

The present study demonstrates that increased spatial heterogeneity measured with RWH, JWH, and TWH in standard 12-lead resting ECGs is a powerful, electrophysiologically sound, independent predictor of SCD. An ultrarapid automated assessment of spatial heterogeneity in left precordial leads could prove useful as a screening tool for stratifying risk for life-threatening arrhythmias even in low-risk populations.

References

1. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. N Engl J Med 2001;345:1473–1482.
2. Weiss JN, Chen PS, Qu Z, Karagueuzian HS, Garfinkel A. Ventricular fibrillation: how do we stop the waves from breaking? Circ Res 2000;87:1103–1107.
3. Antzelevitch C. Heterogeneity and cardiac arrhythmias: an overview. Heart Rhythm 2007;4:964–972.
4. Strauss DG, Mewton N, Verrier RL, et al. Screening entire health system ECG databases to identify patients with arrhythmogenic myocardial substrate at increased risk of death. Circ Arrhythm Electrophysiol 2013;6:1156–1162.
5. Okin PM, Devereux RB, Fabsitz RR, Lee ET, Galloway JM, Howard BV. Principal component analysis of the T wave and prediction of cardiovascular mortality in American Indians: the Strong Heart Study. Circulation 2002;105:714–719.
6. Nearing BD, Verrier RL. Tracking cardiac electrical instability by computing interlead heterogeneity of T-wave morphology. J Appl Physiol 2003;95:2265–2272.
7. Nearing BD, Verrier RL. Multilead template-derived residua of surface ECGs for quantitative assessment of arrhythmia risk. Ann Noninvas Electrocardiol 2015;20:273–281.
8. Zhao SX, Lee LM, Nearing BD, Busso VO, Kwaku KF, Verrier RL. Suppression of calcium-induced repolarization heterogeneity as a mechanism of nitroglycerin's antiarrhythmic action. J Cardiovasc Pharmacol 2006;48:22–29.
9. Verrier RL, Pagotto VP, Kanas AF, Sobrado MF, Nearing BD, Zeng D, Belardinelli L. Low doses of ranolazine and dronedarone in combination exert potent protection against atrial fibrillation and vulnerability to ventricular arrhythmias during acute myocardial ischemia. Heart Rhythm 2013;10:121–127.
10. Bonatti R, Garcia Silva AF, Pereira Batatinha JA, Sobrado LF, Machado AD, Varone BB, Nearing BD, Belardinelli L, Verrier RL. Selective late sodium current blockade with GS-458967 markedly reduces ischemia-induced atrial and ventricular repolarization alternans and ECG heterogeneity. Heart Rhythm 2014;11:1827–1835.
11. Nearing BD, Wellenius GA, Mittleman MA, Josephson ME, Burger AJ, Verrier RL. Crescendo in depolarization and repolarization heterogeneity heralds development of ventricular tachycardia in hospitalized patients with decompensated heart failure. Circ Arrhythm Electrophysiol 2012;5:84–90.
12. Heistaro S. Methodology Report: Health 2000 Survey. In: Helsinki, Finland: National Public Health Institute; 2008.
13. Rapola JM, Virtamo J, Korhonen P, Haapakoski J, Hartman AM, Edwards BK, Heinonen OP. Validity of diagnoses of major coronary events in national registers of hospital diagnoses and deaths in Finland. Eur J Epidemiol 1997;13:133–138.
14. Pencina MJ, D'Agostino RB, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. Stat Med 2011;30:11–21.
15. Elming H, Holm E, Jun L, Torp-Pedersen C, Kober L, Kircshoff M, Malik M, Camm J. The prognostic value of the QT interval and QT interval dispersion in all-cause and cardiac mortality and morbidity in a population of Danish citizens. Eur Heart J 1998;19:1391–1400.
16. Dekker JM, Crow RS, Hannan PJ, Schouten EG, Folsom AR, ARIC Study. Heart rate-corrected QT interval prolongation predicts risk of coronary heart disease in black and white middle-aged men and women: the ARIC study. J Am Coll Cardiol 2004;43:565–571.
17. Porthan K, Viitasalo M, Toivonen L, Havulinna AS, Jula A, Tikkanen JT, Vaananen H, Nieminen MS, Huikuri HV, Newton-Cheh C, Salomaa V, Oikarinen L. Predictive value of electrocardiographic T-wave morphology parameters and T-wave peak to T-wave end interval for sudden cardiac death in the general population. Circ Arrhythm Electrophysiol 2013;6:690–696.
18. Karjalainen J, Reunanen A, Ristola P, Viitasalo M. QT interval as a cardiac risk factor in a middle aged population. Heart 1997;77:543–548.
19. Goldberg RJ, Bengtson J, Chen ZY, Anderson KM, Locati E, Levy D. Duration of the QT interval and total and cardiovascular mortality in healthy persons (the Framingham Heart Study experience). Am J Cardiol 1991;67:55–58.
20. Malik M, Farbom P, Batchvarov V, Hnatkova K, Camm AJ. Relation between QT and RR intervals is highly individual among healthy subjects: implications for heart rate correction of the QT interval. Heart 2002;87:220–228.
21. Day CP, McComb JM, Campbell RW. QT dispersion: an indication of arrhythmia risk in patients with long QT intervals. Br Heart J 1990;63:342–344.
22. Fu GS, Meissner A, Simon R. Repolarization dispersion and sudden cardiac death in patients with impaired left ventricular function. Eur Heart J 1997;18:281–289.
23. Perkiomaki JS, Koistinen MJ, Yli-Mayry S, Huikuri HV. Dispersion of QT interval in patients with and without susceptibility to ventricular tachyarrhythmias after previous myocardial infarction. J Am Coll Cardiol 1995;26:174–179.
24. Manttari M, Oikarinen L, Manninen V, Viitasalo M. QT dispersion as a risk factor for sudden cardiac death and fatal myocardial infarction in a coronary risk population. Heart 1997;78:268–272.
25. Glancy JM, Garratt CJ, Woods KL, de Bono DP. QT dispersion and mortality after myocardial infarction. Lancet 1995;345:945–948.
26. Zabel M, Klingenheben T, Franz MR, Hohnloser SH. Assessment of QT dispersion for prediction of mortality or arrhythmic events after myocardial infarction: results of a prospective, long-term follow-up study. Circulation 1998;97:2543–2550.
27. Coumel P, Maison-Blanche P, Badilini F. Dispersion of ventricular repolarization: reality? Illusion? Significance? Circulation 1998;97:2491–2493.
28. Statters DJ, Malik M, Ward DE, Camm AJ. QT dispersion: problems of methodology and clinical significance. J Cardiovasc Electrophysiol 1994;5:672–685.
29. Surawicz B, Will QT. dispersion play a role in clinical decision-making? J Cardiovasc Electrophysiol 1996;7:777–784.

30. Panikkath R, Reinier K, Uy-Evanado A, Teodorescu C, Hattenhauer J, Mariani R, Gunson K, Jui J, Chugh SS. Prolonged Tpeak-to-Tend interval on the resting ECG is associated with increased risk of sudden cardiac death. Circ Arrhythm Electrophysiol 2011;4:441–447.
31. Zabel M, Acar B, Klingenheben T, Franz MR, Hohnloser SH, Malik M. Analysis of 12-lead T-wave morphology for risk stratification after myocardial infarction. Circulation 2000;102:1252–1257.
32. Stein KM. Noninvasive risk stratification for sudden death: signal-averaged electrocardiography, nonsustained ventricular tachycardia, heart rate variability, baroreflex sensitivity, and QRS duration. Prog Cardiovasc Dis 2008;51:106–117.
33. Verrier RL, Klingenheben T, Malik M, El-Sherif N, Exner DV, Hohnloser SH, Ikeda T, Martínez JP, Narayan SM, Nieminen T, Rosenbaum DS. Microvolt T-wave alternans: physiological basis, methods of measurement, and clinical utility. Consensus guideline by International Society for Holter and Noninvasive Electrocardiology. J Am Coll Cardiol 2011;58:1309–1324.
34. Haissaguerre M, Derval N, Sacher F, et al. Sudden cardiac arrest associated with early repolarization. N Engl J Med 2008;358:2016–2023.
35. Tikkanen JT, Anttonen O, Junttila MJ, Aro AL, Kerola T, Rissanen HA, Reunanen A, Huikuri HV. Long-term outcome associated with early repolarization on electrocardiography. N Engl J Med 2009;361:2529–2537.

CLINICAL PERSPECTIVES

As sudden cardiac death, the leading cause of adult mortality in the industrially developed world, is the first manifestation of underlying cardiac disease in 30%–40% of cases, there is a great need for means to identify subjects at risk. Electrocardiographic heterogeneity provides an accurate, ultrarapid means to estimate sudden cardiac death risk from a standard, resting 12-lead electrocardiogram, which is widely used across the medical system, as demonstrated in the Health 2000 Survey. Accordingly, physicians who use this screen could implement diagnostic and preventive measures.