



Prognostic significance of beat-to-beat variability of spatial heterogeneity of repolarization analyzed from a 5-minute resting electrocardiogram in coronary artery disease ^e

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ABSTRACT

BACKGROUND Data on the prognostic significance of temporal variability of spatial heterogeneity of electrocardiographic repolarization in coronary artery disease (CAD) are limited.

OBJECTIVE The purpose of this study was to evaluate the prognostic value of temporal variability of T-wave morphology analyzed from a 5-minute resting electrocardiogram in CAD.

METHODS The standard deviation (SD) of T-wave morphology dispersion (TMD-SD) and the SD of total cosine R-to-T were analyzed on a beat-to-beat basis from a 5-minute period of the standard resting 12-lead electrocardiogram obtained before the clinical stress test in 1702 patients with angiographically verified CAD and well-preserved left ventricular function.

RESULTS During an average of 8.7 ± 2.2 years of follow-up, 60 patients experienced sudden cardiac death/arrest (SCD/SCA) (3.5%), 69 patients nonsudden cardiac death (NSCD) (4.1%), and 161 patients noncardiac death (9.5%). TMD-SD was significantly higher in patients who experienced SCD/SCA than in other patients (1.72 ± 2.00 vs 1.12 ± 1.75 ; $P = .01$) and higher in patients who succumbed to NSCD than in other patients (1.57 ± 1.74 vs 1.12 ± 1.76 ; $P = .04$), but it did not differ significantly between patients who experienced noncardiac death and those without such an event (1.16 ± 1.42 vs 1.14 ± 1.79 ; $P = .86$). In the Cox multivariable hazards model, TMD-SD retained its significant association with the risk of SCD/SCA (hazard ratio 1.119; 95% confidence interval 1.015–1.233; $P = .024$) but not with the risk of NSCD (hazard ratio 1.089; 95% confidence interval 0.983–1.206; $P = .103$).

CONCLUSION TMD-SD is independently associated with the long-term risk of SCD/SCA in patients with CAD.

KEYWORDS Electrocardiography; T-wave; T-wave morphology; Repolarization; Sudden cardiac death

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Introduction

Sudden cardiac death (SCD) is a significant cause of mortality in the Western world accounting for up to 10%–20% of all deaths.^{1,2} Even in the modern treatment era, coronary artery disease is responsible for up to 70%–80% of all SCDs in the Western world.^{3,4} The implantable cardioverter-defibrillator has proved to be an effective intervention in high-risk individuals in both primary and secondary prevention of SCD.⁵ There is a clear need to develop better discriminating risk stratification models for SCD to guide the efficient use of implantable cardi-

overter-defibrillator therapy. The search for electrocardiographic risk indicators of SCD has gained attention in the past couple of decades. Vectorcardiography-based applications have gained attention, as they use the morphological information of T wave.⁶ Promising results have been obtained in studies considering both temporal and spatial variability in heterogeneity of electrocardiographic repolarization, which suggests that an optimal risk indicator should consider the complete temporospatial phenomena, instead of focusing on just 1 property of heterogeneity of electrocardiographic

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repolarization.⁷⁻⁹ The potential for electrocardiogram (ECG)-based risk predictors of SCD to translate into clinical use is thus well-grounded. We have previously introduced a novel risk indicator for SCD, the standard deviation of T-wave morphology dispersion (TMD-SD), which was found to be an independent risk predictor of SCD when derived from ambulatory Holter recordings of patients with coronary artery disease.¹⁰ In the present study, we analyzed resting ECGs and obtained TMD-SD among several other previously introduced risk indicators that represent both temporal and spatial phenomena in the repolarization phase of the myocardium and investigated their association with SCD and other modes of death.

Methods

Study population

The ARTEMIS (Innovation to Reduce Cardiovascular Complications of Diabetes at the Intersection; can be found at clinicaltrials.gov with the identifier NCT01426685) is an observational prospective cohort study that enrolled patients with angiographically verified coronary artery disease, with a proportion also having type 2 diabetes. Patients were recruited from 2007 through 2012 from the consecutive series of patients undergoing coronary angiography at the Division of Cardiology in Oulu University Hospital. The details of the study protocol and exclusion criteria have previously been described elsewhere.¹¹ A total of 1702 patients were in sinus rhythm and had good quality digital 5-minute resting 12-lead ECGs before a clinical stress test and were included in the present analysis. All recruited patients provided informed consent, and the Northern Ostrobothnia Hospital District Ethical Committee approved the study protocol. The study follows recommendations of the Declaration of Helsinki.

End points of the present study

The primary end point of the present analysis was SCD or resuscitation from sudden cardiac arrest (SCA), whichever occurred first. Secondary end

points were nonsudden cardiac death (NSCD) and noncardiac death (NCD). SCD was defined as cardiac death within 1 hour of the onset of symptoms. *Unwitnessed SCDs* were defined as cases where a patient was last seen alive and well 24 hours before discovery. As per Finnish law, medicolegal autopsy is required in uncertain causes of death, and therefore autopsy records were available in most cases. NSCD was defined as a cardiac death that did not meet the criteria of SCD/SCA. Patients

who experienced death from noncardiac causes were included in the NCD group. The determination of end points used a combination of emergency medical service reports, physician reports, death certificates, data from autopsies, and inquiries to the next of kin. The cause and mode of death were determined by 2 investigators independently, and possible conflicts about the mode of death was resolved by the investigators H.V.H. and M.J.J.

Echocardiography

Echocardiography was performed using the General Vivid 7 ultrasound machine (General Electric Healthcare, Little Chalfont, UK). Transthoracic examinations were carried out in accordance with the general guidelines of the American Society of Echocardiography. The examination included 2-dimensional, M-mode, Doppler echocardiography. Left ventricular ejection fraction (LVEF) was derived using the 2-dimensional method. Left ventricular mass index was obtained using the body surface area equation.

Electrocardiography

Standard digital 12-lead ECGs were obtained for each patient during a 5-minute resting period before the clinical stress test by using CardioSoft version 6.5 (GE Healthcare, Fairfield, CT). Data obtained from the ECGs were analyzed using specifically tailored software made by T.V.K. and written in the MATLAB language (MathWorks Inc., Natick, MA). Before analysis, the ECG recordings were filtered for high-frequency noise in excess of 150 Hz, wall power-line interference at 50 Hz, and baseline wander falling below 0.67 Hz. The 0.67 Hz cutoff frequency was selected because it corresponds to the ventricular rate of 40 beats/min, which was below the minimum heart rate in the population, but high enough frequency to filter out artifacts from baseline wander.

Parameters of T-wave morphology were used to represent the spatial heterogeneity of electrocardiographic repolarization. Analysis was performed beat-to-beat during the 5-minute period. The details of the methodology are described previously.¹⁰

TMD measures the variation in T-wave morphology across different ECG leads, with homogeneous T-wave morphology leading to small values and heterogeneous T-wave morphology increasing the value.¹² TMD is obtained by calculating reconstruction vectors for the independent ECG leads; TMD represents the average angle between all possible reconstruction vector pairs of leads I-II and V₂-V₆ in 3 dimensions, and its values are in degrees.¹³ Total cosine R-to-T (TCRT) estimates the spatial deviation between myocardial repolarization and depolarization wavefronts.¹⁴ Both TMD and TCRT were derived from the same decomposition as described in the original article by Acar et al.¹³ To assess the temporal variability of different T-wave parameters, we calculated SD during the 5-minute period of analysis for uncorrected QT interval, TMD, and TCRT. Through this, the parameters QT-SD, TMD-SD, and TCRT-SD were obtained. These parameters represent both temporal and spatial variability of repolarization.

Abbreviations

ECG: electrocardiogram

IDI: integrated discrimination index

LVEF: left ventricular ejection fraction

NCD: noncardiac death

NSCD: nonsudden cardiac death

SCA: sudden cardiac arrest

SCD: sudden cardiac death

SD: standard deviation

TCRT: total cosine R-to-T

TMD: T-wave morphology dispersion

Statistical analysis

Statistical analyses were performed using version 28 of the IBM SPSS software (IBM Corporation, Armonk, NY). The independent samples *t* test was used to test for statistically significant differences between continuous variables, and the χ^2 test was used likewise for categorical variables. The receiver operating characteristic curve was used to determine the optimal cutoff point for TMD-SD. The Kaplan-Meier survival curves were constructed for TMD-SD to disclose the cumulative proportional probabilities of survival for each different mode of death. The statistical significance of Kaplan-Meier analyses was assessed using the log-rank test. The clinically relevant risk factors that remained significant in the univariable analysis were included in the Cox regression analysis. The risk factors that retained their statistical significance after multivariable adjustments formed the basic clinical risk model for each type of death. The electrocardiographic parameters showing a significant association with a certain mode of death in the univariable analyses were tested one at a time in the final step of the corresponding Cox proportional hazards model as continuous variables. The C-index and integrated discrimination index (IDI) were calculated to assess the discrimination accuracy and net reclassification index to assess the reclassification accuracy of risk markers. A *P* value under .05 was considered significant in statistical analyses.

Results

Patients were followed up for 8.7 ± 2.2 years on average. During that period, 60 patients experienced SCD/SCA (3.5%), 69 patients NSCD (4.1%), and 161 patients NCD (9.5%). Table 1 lists the clinical characteristics that differed significantly between patients who experienced SCD/SCA or succumbed to NSCD or NCD and those without a corresponding event.

Heart rate or heart rate variability measured as the standard deviation of the interbeat intervals of normal sinus beats did not differ significantly when each patient group who experienced different modes of death was compared with a patient group without such an event (Table 2). The average QT interval corrected with Bazett's formula was statistically significantly longer, average TCRT smaller, and average TMD higher in patients with SCD/SCA and those with NSCD than in patients without such an event. QT-SD and TCRT-SD did not differ significantly when each patient group who experienced different modes of death was compared with a patient group without such an event. The values of TMD-SD were significantly higher in patients who experienced SCD/SCA and those who experienced NSCD than in patients without such an event (Table 2). The Kaplan-Meier curves show SCD-free, NSCD-free, and NCD-free survival for patients who had TMD-SD values ≥ 1.48 or < 1.48 (Figure 1) as well as for patients with and without type 2 diabetes separately (Online Supplemental Figures 1 and 2).

When the clinical factors that differed significantly between patients who experienced SCD/SCA and those without

such an event (Table 1) were tested in the Cox regression multivariable hazards model, type 2 diabetes, Canadian Cardiovascular Society class ≥ 2 , left bundle branch block, and triglycerides retained their statistical significance in the model (Table 3). When the clinical factors that were significantly associated with the risk of NSCD in univariable comparisons (Table 1) were analyzed in the Cox multivariable hazards model, age, Canadian Cardiovascular Society class ≥ 2 , lack of antithrombotic medication, triglycerides, and creatinine remained in the model as significant risk factors (Table 3). Of the significant risk factors for NCD in univariable comparisons (Table 1), age, use of diuretic medication, and creatinine retained their significance in the Cox multivariable model (Table 3). After adjustments for the risk factors for the corresponding death classes in the Cox multivariable model, average QT interval corrected with Bazett's formula did not retain its significant association with the risk of SCD/SCA or NSCD, and average TCRT retained the association only with the risk of NSCD. TMD-SD was significantly associated only with the risk of SCD/SCA but not with the risk of NSCD or NCD (Table 3). By contrast, the average TMD retained its significant association with both SCD/SCA and NSCD after the adjustments (Table 3). When dichotomized average TMD and dichotomized TMD-SD were added to the SCD clinical risk model, the C-index increased from 0.70 to 0.73 and IDI (0.0091 [95% confidence interval 0.0018–0.0163]; *P* = .014) and net reclassification index (0.3183 [0.0611–0.5754]; *P* = .015) improved significantly.

Discussion

In our present analysis of patients with coronary artery disease, we found that temporal variability of T-wave morphology, an estimator of temporospatial heterogeneity of repolarization, was independently associated with the risk of SCD. The results held after relevant adjustments with other clinical risk factors, with TMD-SD being the only parameter that retained its association in the multivariable risk model specifically for SCD.

The focus of this analysis was to study both temporal and spatial heterogeneity of repolarization. Until now, studies assessing beat-to-beat variations in T-wave morphology have been less numerous than those investigating solely the spatial plane of repolarization. Beat-to-beat spatiotemporal variability in the T-wave vector has been associated with an increased risk of SCD in a large community-based cohort of >14,000 participants without impaired left ventricular function.⁷ Periodic repolarization dynamics, an electrocardiographic marker of sympathetic activity, has been shown to predict SCD and NSCD in postinfarction patients with reduced LVEF.¹⁵ A case-control study of 200 subjects with SCD with coronary artery disease found out that increased short-term variability of repolarization heterogeneity, represented by the SD of T-wave heterogeneity, was associated with SCD risk.¹⁶ QT-SD and TCRT-SD were not associated with any mode of death in our present analysis. TMD-SD remained a sole specific marker of SCD risk after multivariable adjustments, which is in line with previous studies and our

Table 1 Clinical characteristics of the study patients at baseline

Characteristic	Alive	SCD/SCA	NSCD	NCD
	(n = 1412)	(n = 60)	(n = 69)	(n = 161)
Age (y)	65.6 ± 8.2	68.9 ± 7.8*	73.9 ± 6.9 [†]	72.1 ± 7.4 [‡]
Male gender	970 (68.7)	46 (76.7)	48 (69.6)	123 (76.4)
BMI (kg/m ²)	28.1 ± 4.3	28.8 ± 4.8	29.3 ± 5.4	27.8 ± 4.6
BP, systolic (mm Hg)	146.7 ± 24.0	149.6 ± 23.0	148.7 ± 25.2	148.6 ± 27.7
BP, diastolic (mm Hg)	80.6 ± 11.3	81.7 ± 11.0	79.5 ± 11.6	80.4 ± 13.9
DM2	539 (38.2)	38 (63.3) [‡]	42 (60.9) [‡]	79 (49.1)*
Smoker	117 (8.3)	8 (13.3)	5 (7.2)	12 (7.5)
Alcohol	5.9 ± 6.0	8.7 ± 11.1	7.8 ± 8.2	5.8 ± 6.5
CCS class ≥ 2	539 (38.2)	39 (65.0) [‡]	52 (75.4) [‡]	78 (48.4)
LBBB	37 (2.6)	8 (13.3) [‡]	4 (5.9)	3 (1.9)
RBBB	55 (3.9)	2 (3.3)	5 (7.4)	14 (8.7) [†]
Claudication	75 (5.4)	9 (15.0)*	14 (20.6) [‡]	19 (11.9)*
β-Blocker	1234 (87.5)	55 (91.7)	65 (94.2)	143 (88.8)
ACEI	569 (40.4)	25 (41.7)	30 (43.5)	59 (36.6)
AT2 inhibitor	382 (27.1)	22 (36.7)	22 (31.9)	50 (31.1)
Lipid l.m.	1309 (92.8)	53 (88.3)	60 (87.0)	143 (88.8)
Anti-t.m.	1381 (97.9)	60 (100)	65 (94.2)*	160 (99.4)
Diuretics	399 (28.3)	26 (43.3)	39 (56.5) [‡]	80 (49.7) [‡]
Ca blocker	321 (22.7)	17 (28.3)	23 (33.3)*	38 (23.6)
Nitrates	487 (34.5)	32 (53.3) [†]	42 (60.9) [‡]	68 (42.2)
Anti-a.m.	11 (0.8)	0 (0)	2 (2.9)	1 (0.6)
Asthma/COPD med.	110 (7.8)	7 (11.7)	7 (10.1)	18 (11.2)
GHbA1c (%)	6.2 ± 0.9	6.7 ± 1.5 [†]	6.9 ± 1.4 [‡]	6.6 ± 1.1 [‡]
hsCRP (mg/L)	1.9 ± 4.4	3.9 ± 7.1	3.5 ± 5.1*	2.5 ± 4.8
fS-Chol (mmol/L)	4.0 ± 0.9	4.3 ± 1.0*	4.1 ± 0.9	3.9 ± 0.8
fS-HDL-Chol (mmol/L)	1.3 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.3 ± 0.3
fS-LDL-Chol (mmol/L)	2.3 ± 0.8	2.5 ± 0.9 [†]	2.4 ± 0.8	2.2 ± 0.7
fS-Trigly (mmol/L)	1.4 ± 0.8	1.8 ± 1.4*	1.7 ± 0.9*	1.3 ± 0.6 [†]
Crea (μmol/L)	77.7 ± 17.1	82.2 ± 23.0	104.0 ± 48.0 [‡]	87.2 ± 27.5 [‡]
U-alb/crea (mg/mmol)	1.7 ± 4.8	2.9 ± 6.0	9.4 ± 32.1	2.7 ± 6.6
LVEF (%)	64.8 ± 8.3	59.7 ± 12.8 [†]	61.1 ± 12.8*	65.3 ± 9.4
LVMl (g/m ²)	105.7 ± 26.1	120.4 ± 31.5 [†]	121.6 ± 34.4 [‡]	108.9 ± 25.2
LVEDD (mm)	50.3 ± 5.7	52.2 ± 9.2	52.4 ± 8.3*	48.9 ± 6.3 [†]
LVESD (mm)	31.9 ± 5.8	36.0 ± 9.7 [†]	35.7 ± 9.6 [†]	31.4 ± 6.8

Values are presented as mean ± SD or as n (%).

ACEI = angiotensin-converting enzyme inhibitor; alcohol = alcohol consumption in restaurant portions per week; anti-a.m. = antiarrhythmic medication; anti-t.m. = antithrombotic medication; asthma/COPD med- = medication for asthma or chronic obstructive pulmonary disease; AT2 = angiotensin II receptor; BMI = body mass index; BP = blood pressure; CCS class = Canadian Cardiovascular Society class of angina pectoris; Crea = creatinine; DM2 = type 2 diabetes mellitus; fS-Chol = fasting serum total cholesterol; fS-HDL-Chol = fasting serum high-density lipoprotein cholesterol; fS-LDL-Chol = fasting serum low-density lipoprotein cholesterol; fS-Trigly = fasting serum triglyceride; GHbA1c = glycated hemoglobin A_{1c}; hsCRP = high-sensitivity C-reactive protein; LBBB = left bundle branch block; lipid l.m. = lipid-lowering medication; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVMl = left ventricular mass index; NCD = noncardiac death; NSCD = nonsudden cardiac death; nitrates = long-acting nitrates; RBBB = right bundle branch block; SCA = sudden cardiac arrest; SCD = sudden cardiac death; U-alb/crea = urine albumin-creatinine ratio.

*P < .05,

[†]P < .01,

[‡]P < .001 when comparing the characteristics of patients with a certain mode of death with those of patients without such an event.

previous results from the analysis of a 10-minute period of ambulatory Holter recordings, further underlining the notion that an optimal risk indicator for SCD should take into account temporospatial phenomena as a whole.¹⁰

Our results suggest that beat-to-beat variability of T-wave morphology provides prognostic information about SCD risk and could help better discriminate those patients who are at the highest risk, if combined with other risk markers in the current risk models. Type 2 diabetes and left bundle branch block contributed to the risk of SCD. However, TMD-SD retained its statistical power in predicting SCD even after relevant adjustments with other clinical risk factors, such as type 2 diabetes and left bundle branch block. Furthermore,

when TMD-SD and TMD were added to the SCD clinical risk model, which included type 2 diabetes and left bundle branch block, the C-index, IDI, and net reclassification index improved markedly. More accurate risk models could help optimize therapy, such as implantable cardioverter-defibrillator therapy, especially for the vast majority of patients with coronary artery disease who have no history of myocardial infarction or reduced LVEF.¹⁷

Traditional theoretical models of SCD in coronary artery disease have underlined the importance of acute plaque rupture in starting the electrophysiological cascade, which eventually leads to ventricular tachyarrhythmia and SCD. However, this notion has recently been challenged by an

Table 2 Baseline electrocardiographic parameters

Parameter	Alive	SCD/SCA	NSCD	NCD
	(n = 1412)	(n = 60)	(n = 69)	(n = 161)
HRa (beats/min)	61.8 ± 9.5	64.4 ± 11.9	62 ± 10	63 ± 11
SDNN (ms)	73.2 ± 57.7	81.4 ± 64.8	90.2 ± 67.0	84.1 ± 69.1
Avg QTc (ms)	464.6 ± 28.0	476.0 ± 25.5 [†]	478.1 ± 38.1 [†]	470.3 ± 32.2
QT-SD (ms)	1.64 ± 1.31	1.69 ± 1.32	1.52 ± 1.26	1.67 ± 1.57
Avg TCRT	0.3930 ± 0.6408	0.2193 ± 0.6191 [*]	0.0484 ± 0.6682 [‡]	0.3535 ± 0.6471
TCRT-SD	0.0396 ± 0.0886	0.0524 ± 0.0873	0.0383 ± 0.0572	0.0428 ± 0.0847
Avg TMD (deg)	15.4 ± 17.4	26.6 ± 23.4 [†]	28.5 ± 24.0 [‡]	19.2 ± 19.6
TMD-SD (deg)	1.09 ± 1.78	1.72 ± 2.00 [*]	1.57 ± 1.74 [*]	1.16 ± 1.42

Values are presented as mean ± SD.

See the Methods section for details.

Avg QTc = average QT interval corrected with Bazett's formula; Avg TCRT = average total cosine R to T (total cosine R to T is determined by calculating the cosine of the angle between the main vectors of QRS and T-wave loops); Avg TMD = average T-wave morphology dispersion (T-wave morphology dispersion is determined by calculating the average angle between all possible reconstruction vector pairs of limb leads I–II and chest leads V₂–V₆ in 3-dimensional space and it is expressed in degrees); HRa = average heart rate during the 5-min period of the resting electrocardiogram before an exercise test; NCD = noncardiac death; NSCD = nonsudden cardiac death; QT-SD = standard deviation of uncorrected QT interval during the 5-min period of analysis; SCA = sudden cardiac arrest; SCD = sudden cardiac death; SDNN = standard deviation of all normal-to-normal RR intervals during the 5-min period of analysis; TCRT-SD = standard deviation of the total cosine R to T analyzed from the 5-min period of the resting 12-lead electrocardiogram before an exercise test; TMD-SD = standard deviation of the T-wave morphology dispersion analyzed from the 5-min period of the resting 12-lead electrocardiogram before an exercise test.

**P* < .05

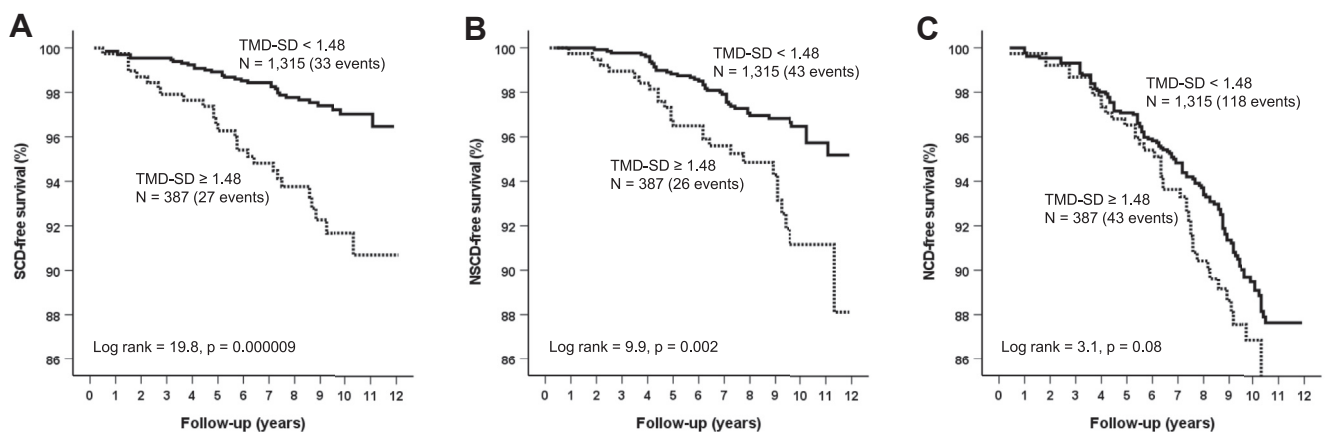
[†]*P* < .01

[‡]*P* < .001 when comparing the characteristics of patients with a certain mode of death with those of patients without such an event.

analysis of 600 autopsy-verified SCD victims whose death was attributable to coronary artery disease, in which less than half of the SCD victims had evidence of acute plaque complication, but almost all the victims had myocardial fibrosis independent of specific plaque histology.¹⁸ This study broadened the spectrum of ischemic causes of SCD and suggested that an interplay between preexisting myocardial fibrosis and acute ischemia is probably more relevant in the development of SCD than plaque complications alone. Concurrently, it has been observed that parameters of P-wave and T-wave heterogeneity are associated with myocardial fibrosis, an observation that suggests that heterogeneity of atrial depolarization and ventricular repolarization could

be indicators of the arrhythmic substrate arising from myocardial fibrosis.¹⁹

The strengths of our study include a long follow-up time and angiographical verification of the coronary artery status. However, there were limitations as well. The number of SCD victims was relatively small. We did not validate our cutoff point for TMD-SD in a separate population; in contrast, we used only continuous values of TMD-SD in the Cox regression analysis. Our study also excluded patients with New York Heart Association class IV and planned or existing implantable cardioverter-defibrillator, a subpopulation that would likely have had an increased heterogeneity of repolarization. The number of patients fulfilling these exclusion criteria was small, however.

**Figure 1**

Kaplan-Meier curves showing (A) sudden cardiac death (SCD)-free survival, (B) nonsudden cardiac death (NSCD)-free survival, and (C) noncardiac death (NCD)-free survival for patients with the standard deviation of T-wave morphology dispersion (TMD-SD) values ≥ 1.48 or < 1.48. The cutoff point was determined from the receiver operating characteristic curve.

Table 3 Univariable and multivariable predictors of SCD, NSCD, and NCD

Variable	SCD		NSCD		NCD	
	HR	95 % CI	HR	95 % CI	HR	95 % CI
Age						
uv	1.040	1.007–1.074*	1.154	1.112–1.198 [‡]	1.109	1.084–1.134 [‡]
mv	1.031	0.995–1.067	1.122	1.078–1.169 [‡]	1.096	1.071–1.121 [‡]
DM II						
uv	2.481	1.466–4.199 [‡]	2.143	1.316–3.492 [‡]	1.389	1.020–1.893*
mv	1.950	1.134–3.353*	1.322	0.707–2.472	1.226	0.841–1.787
CCS class ≥ 2						
uv	2.911	1.711–4.952 [‡]	4.830	2.787–8.370 [‡]		
mv	2.545	1.491–4.347 [‡]	2.840	1.594–5.060 [‡]		
LBBB						
uv	5.414	2.572–11.399 [‡]				
mv	5.013	2.376–10.578 [‡]				
RBBB						
uv					1.702	0.922–3.139
mv					1.728	0.991–3.015
Claudication						
uv	2.493	1.227–5.064*	3.765	2.089–6.786 [‡]	1.889	1.170–3.049 [‡]
mv	1.209	0.562–2.603	1.570	0.796–3.099	1.430	0.870–2.353
Anti-t.m.						
uv			0.392	0.143–1.078		
mv			0.285	0.102–0.793*		
Diuretics						
uv			3.043	1.882–4.921 [‡]	2.260	1.659–3.078 [‡]
mv			1.126	0.647–1.957	1.700	1.235–2.340 [‡]
Ca blocker						
uv			1.684	1.019–2.783*		
mv			1.011	0.579–1.764		
Nitrates						
uv	2.008	1.209–3.335 [‡]	2.686	1.652–4.365 [‡]		
mv	1.639	0.945–2.843	1.251	0.725–2.159		
GHbA1c						
uv	1.334	1.106–1.610 [‡]	1.459	1.247–1.707 [‡]	1.204	1.057–1.372 [‡]
mv	1.020	0.782–1.330	1.169	0.922–1.482	1.118	0.950–1.317
hsCRP						
uv			1.032	1.008–1.056 [‡]		
mv			1.031	0.997–1.067		
fS-Chol						
uv	1.450	1.143–1.838 [‡]				
mv	1.001	0.517–1.939				
fS-LDL-Chol						
uv	1.470	1.128–1.915 [‡]				
mv	1.524	0.751–3.091				
fS-Trigly						
uv	1.511	1.234–1.849 [‡]	1.423	1.146–1.768 [‡]	0.752	0.581–0.972*
mv	1.424	1.128–1.798 [‡]	1.526	1.157–2.012 [‡]	0.760	0.571–1.012
Crea						
uv			1.021	1.017–1.025 [‡]	1.014	1.009–1.018 [‡]
mv			1.016	1.011–1.021 [‡]	1.006	1.001–1.012*
LVEF						
uv	0.947	0.926–0.968 [‡]	0.956	0.935–0.978 [‡]		
mv	0.984	0.955–1.014	0.992	0.962–1.022		
LVMI						
uv	1.016	1.009–1.024 [‡]	1.018	1.011–1.025 [‡]		
mv	1.004	0.994–1.014	1.002	0.991–1.012		
LVEDD						
uv			1.061	1.023–1.102 [‡]	0.963	0.937–0.989 [‡]
mv			1.029	0.961–1.101	0.979	0.954–1.006
LVESD						
uv	1.080	1.047–1.114 [‡]	1.077	1.045–1.110 [‡]		
mv	1.042	0.994–1.093	1.040	0.980–1.104		
Avg QTc						

Table 3 Continued

Variable	SCD		NSCD		NCD	
	HR	95 % CI	HR	95 % CI	HR	95 % CI
uv	1.012	1.004–1.020 [†]	1.014	1.006–1.021 [‡]		
mv	1.002	0.993–1.011	1.005	0.998–1.012		
Avg TCRT						
uv	0.670	0.466–0.964*	0.470	0.338–0.654 [‡]		
mv	0.910	0.605–1.371	0.614	0.439–0.857 [†]		
Avg TMD						
uv	1.023	1.013–1.034 [‡]	1.026	1.016–1.035 [‡]		
mv	1.014	1.002–1.025*	1.020	1.011–1.030 [‡]		
TMD-SD						
uv	1.129	1.036–1.231 [†]	1.105	1.008–1.210*		
mv	1.119	1.015–1.233*	1.089	0.983–1.206		

CI = confidence interval; HR = hazard ratio; mv = multivariable; uv = univariable; other abbreviations as in Tables 1 and 2.

* $P < .05$

[†] $P < .01$

[‡] $P < .001$ when comparing the characteristics of patients with a certain mode of death with those of patients without such an event. The Cox regression analysis (uv and mv) was performed only for the clinical factors that differed significantly between the group comparisons of the corresponding death class (Table 1). These clinical factors were partly different for each death class; therefore, there are empty spaces in this table. Those clinical factors that remained significant in the multivariable Cox regression analysis formed the clinical risk model for the corresponding death class. The repolarization variability parameters were tested one at a time in these death class-specific risk models, and uv and mv HRs were shown only when the parameter differed significantly in the group comparisons of the corresponding death class (Table 2).

Conclusion

TMD-SD, representing temporal variability of spatial heterogeneity of repolarization, analyzed from a 5-minute 12-lead ECG, was an independent and specific predictor of SCD in patients with angiographically verified coronary artery disease and well-preserved left ventricular function. Future studies are needed to confirm these findings in separate patient populations.

Appendix

Supplementary Data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.hrthm.2024.02.052>.

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