



ORIGINAL ARTICLE

Temporal variability of T-wave morphology and risk of sudden cardiac death in patients with coronary artery disease

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Abstract

Background: The possible relationship between temporal variability of electrocardiographic spatial heterogeneity of repolarization and the risk of sudden cardiac death (SCD) in patients with coronary artery disease (CAD) is not completely understood.

Methods: The standard deviation of T-wave morphology dispersion (TMD-SD), of QRST angle (QRSTA-SD), and of T-wave area dispersion (TW-Ad-SD) were analyzed on beat-to-beat basis from 10 min period of the baseline electrocardiographic recording in ARTEMIS study patients with angiographically verified CAD.

Results: After on average of 8.6 ± 2.3 years of follow-up, a total of 66 of the 1,678 present study subjects (3.9%) had experienced SCD or were resuscitated from sudden cardiac arrest (SCA). TMD-SD was most closely associated with the risk for SCD and was significantly higher in patients who had experienced SCD/SCA compared with those who remained alive (3.61 ± 2.83 vs. 2.64 ± 2.52 , $p = .008$, respectively), but did not differ significantly between the patients who had experienced non-SCD ($n = 71$, 4.2%) and those who remained alive (3.20 ± 2.73 vs. 2.65 ± 2.53 , $p = .077$, respectively) or between the patients who succumbed to non-cardiac death ($n = 164$, 9.8%) and those who stayed alive (2.64 ± 2.17 vs. 2.68 ± 2.58 , $p = .853$). After adjustments with relevant clinical risk indicators of SCD/SCA, TMD-SD still predicted SCD/SCA (HR 1.107, 95% CIs 1.035–1.185, $p = .003$).

Conclusions: Temporal variability of electrocardiographic spatial heterogeneity of repolarization represented by TMD-SD independently predicts long-term risk of SCD/SCA in patients with CAD.

KEYWORDS

electrocardiography, repolarization, sudden cardiac death, T-wave, T-wave morphology

This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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1 | INTRODUCTION

Sudden cardiac death (SCD) is defined as unexpected death from a cardiac cause that occurs within one hour of symptom onset when the start of symptoms is witnessed or when unwitnessed, within 24 hr when the patient was last observed to be in normal health (Mozaffarian et al., 2015). Because the vast majority of SCD victims have coronary artery disease (CAD), many risk factors of SCD overlap with those of CAD, such as age, hypertension, left ventricular hypertrophy, intraventricular conduction block, glucose intolerance, and smoking (Zipes & Wellens, 1998). However, none of these traditional cardiovascular risk factors are specific to SCD, because all CAD patients also face the competing risk of non-sudden cardiac death (NSCD) (Deyell et al., 2015). The current clinical risk stratification models for SCD in patients with CAD mainly rely on decreased left ventricular ejection fraction and past history of myocardial infarction (MI), as these two conditions are the biggest population attributable risk factors for SCD (Rea et al., 2004). These evaluation methods, however, still fail to outline the largest subgroup of CAD patients that are at high risk for SCD: the ones that do not have ventricular dysfunction or any other manifestation of CAD prior to their sudden death (Deyell et al., 2015). During recent decades, three-dimensional vectorcardiography (VCG) has attracted attention as a potential method to gain new prognostic parameters for cardiovascular risk assessment (Hasan & Abbott, 2016). Spatiotemporal changes in the electrophysiology of myocardium can be measured using VCG-derived parameters that yield information beyond that of the conventional electrocardiogram (ECG) (Verrier & Huikuri, 2017). Although the ECG has brought well established and widely available indices, such as the QT interval, that characterize electrocardiographic repolarization, the methodology has been limited by the fact that it is one-dimensional (i.e., consisting of only the magnitude of heart signal) and does not reveal three-dimensional features of electrocardiographic repolarization (Hasan & Abbott, 2016). The VCG, on the other hand, goes further and measures both direction and magnitude of cardiac electrical activity in spatial planes, thus allowing a much more complete outlook on cardiac repolarization dynamics (Yang et al., 2012). Current VCG methodology is not without its own limitations, which include the need to further validate existing parameters, lack of VCG measurement options routinely available in contemporary electrocardiographic analysis software, and the fact that most clinicians still are not familiar with the technology (Hasan & Abbott, 2016). A study of temporal variability in repolarization heterogeneity by using VCG parameters is an emerging area of investigation, though its full potential is yet to be explored (Hasan & Abbott, 2016). Several parameters describing only the spatial aspect in heterogeneity of electrocardiographic repolarization have been shown to yield prognostic information in earlier studies, but the significance of results has varied between analyses (Pirkola et al., 2018; Porthan et al., 2013; Zabel et al., 2000, 2002). In contrast, previous studies combining both temporal and spatial analysis of repolarization heterogeneity have consistently

suggested that there is a relationship between labile repolarization of myocardium and increased risk of life-threatening arrhythmias and that the relationship is more profound than spatial analyses alone can decipher (Kenttä et al., 2012; Perkiömäki et al., 2002; Waks et al., 2015). However, studies investigating dynamics of T-wave morphology in CAD patients with well-preserved left ventricular function have been scarce to date, and thus, the prognostic value of parameters describing the temporal variability of electrocardiographic repolarization heterogeneity has not been well established in the current treatment era of CAD (Waks et al., 2015). Therefore, the present study was aimed to test the hypothesis that beat-to-beat variation of T-wave morphology representing temporal variability in heterogeneity of electrocardiographic repolarization predicts SCD in patients with CAD. The discovery of novel, more efficient risk markers of SCD could also facilitate risk stratification in populations beyond CAD patients. Finally, the improvement of risk assessment models would make it possible to better guide implementation of effective but resource-intensive therapeutic interventions, such as the application of implantable cardioverter-defibrillators (ICD).

2 | METHODS

2.1 | Study population

The Innovation to Reduce Cardiovascular Complications of Diabetes at the Intersection (ARTEMIS) study database consists of 1,946 patients with angiographically verified CAD with or without diabetes. The database was collected between August 2007 and November 2011, and patients were defined having CAD if they had angiographically verified stenosis of at least 50% in one or more major coronary vessels. The data related to the present study are freely accessible by contacting the corresponding author. Risk assessments were done and inclusion status determined from 3 to 6 months after the coronary angiography or the last revascularization. Nondiabetic patients were matched with the patients with diabetes according to age, sex, prior myocardial infarction, and revascularization. The World Health Organization criteria were used to diagnose diabetes. At the initial visit, all the patients without the diagnosis of diabetes had an oral 2-hr glucose tolerance test. The details of the study protocol and population are described elsewhere (Junttila et al., 2018; Kiviniemi et al., 2019).

The study took place at the Division of Cardiology of the University Hospital of Oulu (registered at clinicaltrials.gov; identifier number NCT01426685). The ARTEMIS study was carried out in accordance to the recommendations of Declaration of Helsinki, and study protocol was reviewed and approved by the ethical committee of Northern Ostrobothnia Hospital District. All study subjects had to provide an informed consent before they were included in the study. The study exclusion criteria were age under 18 or over 80 years, New York Heart Association (NYHA) class IV or Canadian Cardiovascular Society (CCS) class IV, planned

or existing ICD, life expectancy under one year, pregnancy, end-stage renal dysfunction requiring dialysis, and being otherwise unfit for the study due to physical or psychological reasons, or due to doubted compliance. The patients had regular follow-up controls due to their CAD. Questionnaires and telephone calls were used during the follow-up period to gather data about the prevailing situation. Digital 12-lead ECGs were obtained from 3 to 6 months after the coronary angiography during the ARTEMIS study. A total of 1,678 patients were in sinus rhythm and had good quality ECG recordings and were included in the present analysis. The patients with non-sinus rhythm or low quality ECG recordings were excluded from the present study.

2.2 | Endpoints of the current study

The endpoints of the study were SCD, NSCD, and non-cardiac death (NCD). SCD was the primary endpoint, defined as death occurring within one hour after the onset of symptoms, or within 24 hr of the last witnessed moment of being alive, if the onset of symptoms took place unwitnessed. Patients resuscitated from sudden cardiac arrest (SCA) were treated as having experienced SCD. NSCD and NCD served as the secondary endpoints of the study. NSCD included patients that died of cardiac causes but did not meet the criteria for SCD. Deaths without a cardiac cause were classified as NCD.

2.3 | Electrocardiography

The study patients underwent a digital 12-lead ambulatory ECG recording 3–6 months after the coronary angiography. The sampling rate of the ECG recordings was 256 Hz. The recording device used was Medilog AR12 (Huntleigh Healthcare, Newtownabbey, UK), and the record duration was 24 hr. Spatial heterogeneity of repolarization was analyzed from each successive beat during a 10-min period. Repolarization irregularity has been shown to be greatest in the morning; therefore, the time period for analyses was chosen to be during the daytime hours, to avoid circadian variation in repolarization (Smetana et al., 2002). It was concluded that randomly but systematically selected 10-min periods of ECG recordings would represent the average beat-to-beat temporal variability of electrocardiographic spatial heterogeneity of repolarization in patients who remained alive compared with patients who experienced SCD, NSCD, or NCD (Tereshchenko and Feeny, 2016). The predefined criteria for selection of 10-min period for analysis were the following. The 10-min period had to be selected between noon and 6 p.m. from the beginning of an hour where heart rate was between 50 and 100/min in the 10 min period. The beginning of the hour was selected in chronological order among the hours when the heart rate criterion for the 10-min period was first fulfilled.

2.4 | Analysis of electrocardiographic spatial heterogeneity of repolarization

Data obtained from the ECG recordings were analyzed using a custom-made software package written in Matlab (MathWorks inc, Natick, MA). The Holter recordings were first filtered in order to remove high-frequency noise (>150 Hz), power-line interference (at 50 Hz), and baseline wander (<0.67 Hz). The 0.67 Hz cut-off frequency of baseline wander corresponds with ventricular rate of 40 bpm, which was below the lowest heart rate in the population, but high enough to effectively filter baseline wander. Spatial heterogeneity of repolarization was analyzed from each successive beat during a 10-min period using modified moving average (MMA) algorithm with an update factor of 1/10 (i.e., the fraction of morphology change that an incoming beat can contribute). The MMA recursive averaging algorithm works by calculating an initial template for each ECG lead, and this template is then updated recursively with each successive beat. Each incoming beat is compared to the current template point by point, and if the difference is more than $32 \mu\text{V}$, a point is only updated by $32 \mu\text{V}$ toward the new sample (\mp). If the value of an incoming sample is within $32 \mu\text{V}$, the point is updated by 1/10 of the difference. The MMA algorithm was applied to every ECG lead. This type of averaging has been shown to be very robust and is widely used, for example, in T-wave alternans measurements (Nearing & Verrier, 2002). However, in contrast to the MMA-based T-wave alternans estimation, where the beat averaging is done for alternate beats, here the algorithm is applied to consecutive beats in order to produce a single average beat at each beat location. Residual noise was assessed from the TP segment of each beat by the custom-made software used to analyze the ECG recordings. If residual noise exceeded the threshold of $40 \mu\text{V}$, the beat was replaced with the last valid beat morphology. The software then automatically calculated T-wave morphology dispersion (TMD) using methodology described earlier in detail (Acar et al., 1999). T-wave vector represents the sum repolarization wavefront in the myocardium at a given time during the repolarization phase of cardiac cycle, and this vector goes through constant change in direction and magnitude as the cardiac repolarization runs through its course. T-wave loop is then obtained by drawing a line between each individual momentary T-wave vector head during a complete repolarization cycle. TMD is based on the T-wave loop and estimates the variation of T-wave morphology between individual ECG leads (Porthan et al., 2013). First, reconstruction vectors representing the eight independent ECG leads are calculated onto the two-dimensional T-wave loop. TMD is then obtained by calculating the average angle between all possible reconstruction vector pairs of limb leads I-II and chest leads V2–V6 in three-dimensional space, and it is expressed in degrees (Acar et al., 1999). Similar T-wave morphologies between different leads result in a small TMD value, whereas spatial heterogeneity due to abnormal repolarization increases this value. The spatial angle between the main QRS vector and the main T-wave vector (QRSTA) was determined from the QRS and T-wave

loops. QRSTA reflects the spatial angle between the depolarization and repolarization wavefronts and includes prognostic information (Kenttä et al., 2011). T-wave area dispersion (TW-Ad) was obtained from leads I, II, V4-V6. T-wave area under baseline was considered negative. The average T-wave area was divided by the maximum absolute T-wave area within leads I, II, V4 to V6. TW-Ad describes dispersion of T-wave area and shape between the leads I, II, V4-6, that is, spatial heterogeneity of electrocardiographic repolarization (Kenttä et al., 2018). QT interval was measured from the beginning of QRS complex to the end of T wave. QT interval was corrected for heart rate by the Bazett's formula (QTc).

2.5 | Analysis of temporal variability of electrocardiographic spatial heterogeneity of repolarization

TMD, QRSTA, and TW-Ad were analyzed on beat-to-beat basis, and the temporal variability of TMD, QRSTA, and TW-Ad was evaluated using standard deviation of TMD (TMD-SD), QRSTA (QRSTA-SD), and TW-Ad (TW-Ad-SD). TMD-SD, QRSTA-SD, and TW-Ad-SD represent the temporal variability of electrocardiographic spatial heterogeneity of repolarization. Beats that had RR interval less than 80% or more than 120% of the preceding valid RR interval were initially flagged as ectopic beats by the Holter analysis software (Medilog, Darwin). All flagged beats were then manually reviewed/edited by a trained research nurse/physician to get the final decision on the beat template. Ectopic beats (originating from outside the sinus node) were identified and excluded from the analysis in this study. Extra-systolic beats were replaced by an averaged beat from the adjacent accepted template.

2.6 | Echocardiography

Echocardiography was performed using the General Vivid 7 ultrasound instrument (General Electric Healthcare, Little Chalfont, UK). Two-dimensional, M-mode, and Doppler echocardiographies were performed. Left ventricular ejection fraction (LVEF) was assessed using the two-dimensional method. Left ventricular mass (LVM) was derived from the following formula: $LVM = 0.8 \times 1.04 \times [(IVS + LVID + PWT)^3 - LVID^3] + 0.6$ g, where IVS is interventricular septum, LVID is left ventricular internal diameter, and PWT is posterior wall thickness, with all measurements performed at end-diastole. Left ventricular mass index (LVMI) was calculated using the body surface area (BSA) formula, where left ventricular mass is divided by both BSA and squared height.

2.7 | Statistical analysis

Analyses were carried out using IBM SPSS version 25 (IBM SPSS, Armonk, NY, USA). In the univariate analyses, baseline

parameters were compared between those who experienced a certain mode of death and those who remained alive/experienced another mode of death. The independent samples *t* test was used to assess the statistical significance of differences between continuous variables, and Levene's test was used to determine the equality of variances. For categorical variables, the chi-square test was used in conjunction with Fisher's exact test. The clinically relevant risk factors that remained significant in the univariate comparisons between patients with different modes of death, respectively, and patients who remained alive/experienced another mode of death were added to the multivariate Cox proportional hazards model. After multivariate adjustments, the risk factors that retained their significant association with each mode of death formed the basis for a corresponding clinical risk model for each type of death. The electrocardiographic parameters that had a significant univariate association with a mode of death were tested in the final step of the corresponding clinical model one at a time as a continuous variables. Specific follow-up times were applied to each patient individually during the Cox regression analysis, and case-specific follow-up times were used in the Kaplan–Meier survival analysis. To assess improvement in discrimination accuracy, the C-index was calculated for the clinical risk model of SCD. The Kaplan–Meier survival curves were used to demonstrate the cumulative proportional probabilities of survival for different modes of death when the patients were grouped according to dichotomized values of TMD-SD. The statistical significance of the separation of the curves was evaluated using the log-rank test. The cutoff point for the curves was optimized for SCD from the receiver operating characteristics (ROC) curves at a point where the sum of sensitivity and specificity was the greatest. A *p*-value <.05 was considered significant in the analyses.

3 | RESULTS

After on average of 8.6 ± 2.3 years of follow-up, a total of 66 patients (3.9%) had experienced SCD or were resuscitated from SCA. The other modes of death consisted of 71 patients dying of NSCD (4.2%) and 164 (9.8%) patients succumbing to NCD. The causes of NCD included malignant diseases (4%), infections (2%), cerebral infarction/hemorrhage (0.8%), trauma/accident (0.7%), severe neurologic disease (0.6%), chronic pulmonary disease (0.4%), end-stage dementia (0.2%), end-stage renal disease (0.2%), pulmonary embolism (0.1%), peripheral artery disease (0.1%), chronic liver disease (0.1%), intoxication (0.1%), and abdominal vascular disease (0.1%). There was no significant difference in the number of ectopic beats in the victims of SCD compared with the other study subjects (7 ± 24 vs. 3 ± 14 , $p = .15$, respectively). The total number of ectopic beats was small, and most of the study patients (71%) did not have any ectopic beats in the analyzed segment. A total of 1,678 patients were analyzed before stratifying.

TABLE 1 Clinical characteristics of the study patients at baseline

Variable	Alive n = 1,377	SCD/SCA n = 66	NSCD n = 71	NCD n = 164
Age (years)	65.8 ± 8.4	69.6 ± 7.6 [†]	73.9 ± 7.3 [‡]	72.3 ± 7.2 [‡]
Male gender (%)	67.5	72.7	70.4	77.4 [*]
BMI (kg/m ²)	28.2 ± 4.6	28.6 ± 4.8	29.3 ± 5.6	27.8 ± 4.3
BP, systolic (mmHg)	147.0 ± 24.1	148.9 ± 22.8	148.6 ± 23.7	148.9 ± 27.8
BP, diastolic (mmHg)	80.4 ± 11.1	81.2 ± 11.3	79.3 ± 11.1	80.9 ± 13.7
Type II diabetes (%)	38.7	66.7 [‡]	64.8 [‡]	52.4 [†]
Smoker (%)	8.5	13.6	5.6	7.9
Alcohol	5.7 ± 5.7	8.8 ± 10.6	8.8 ± 8.7	7.8 ± 12.2
CCS ≥ 2 (%)	38.5	65.2 [‡]	73.2 [‡]	51.8 [†]
LBBB (%)	3.0	13.6 [†]	8.6 [*]	3.7
RBBB (%)	4.1	4.5	5.7	12.2 [‡]
β-blocker (%)	87.6	89.4	93.0	90.9
ACEI (%)	40.0	43.9	46.5	37.8
AT2 (%)	28.2	33.3	32.4	29.3
Lipid l.m. (%)	93.2	87.9	87.3	88.4
Anti-t.m. (%)	98.0	100	94.4 [*]	99.4
Diuretics (%)	29.7	47.0 [*]	57.7 [‡]	51.2 [‡]
Ca-blocker (%)	23.8	28.8	35.2 [*]	26.8
Nitrates (%)	34.3	56.1 [†]	59.2 [‡]	42.7
Anti-a.m. (%)	0.7	0	2.8	0.6
LVEF (%)	64.6 ± 8.5	59.5 ± 13.0 [†]	61.9 ± 13.4	64.5 ± 10.1
LVMI (g/m ²)	106.3 ± 26.6	119.4 ± 31.5 [‡]	121.0 ± 35.5 [†]	110.2 ± 26.4
LVEDD (mm)	50.4 ± 5.8	52.1 ± 9.1	51.7 ± 8.0	48.9 ± 6.3 [†]

Note: The values are mean ± SD or percentages.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; alcohol, alcohol consumption in restaurant portions per week; anti-a.m., anti-arrhythmic medication; anti-t.m., anti-thrombotic medication; AT2, angiotensin II receptor inhibitor; BMI, body mass index; BP, blood pressure; CCS, Canadian Cardiovascular Society grading of angina pectoris; LBBB, left bundle branch block; lipid l.m., lipid lowering medication; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NCD, non-cardiac death; NSCD, non-sudden cardiac death; Nitrates, long-acting nitrates; RBBB, right bundle branch block; SCA, resuscitated from sudden cardiac arrest; SCD, sudden cardiac death.

**p* < .05,

[†]*p* < .01,

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

3.1 | Association of baseline factors with sudden cardiac, non-sudden cardiac, and non-cardiac death

The patients who experienced SCD/SCA were older, had higher prevalence of type II diabetes, had worse CCS class, presented with left bundle branch block (LBBB) more frequently, were more often on diuretics and long-acting nitrates medication, had lower LVEF, and higher LVMI compared to those who remained alive (Table 1). The associations of baseline clinical factors with NSCD and NCD are presented in Table 1. Temporal variability of T-wave morphology represented by TMD-SD was significantly higher in patients who experienced SCD/SCA compared with patients who stayed alive. However, TMD-SD did not differ significantly between the patients who succumbed to NSCD and those who remained alive or between

the patients who died due to non-cardiac causes and those who survived. QRSTA-SD did not differ significantly between the patients who experienced any mode of death and the other patients. Those who died because of NSCD or NCD had higher values of TW-Ad-SD compared with patients who remained alive. TMD and QTc had significant association with all modes of death. The patients who experienced SCD had higher heart rate in the analyzed 10-min period than those who survived. There was no significant difference in heart rate variability in patients who remained alive when compared with patients who experienced SCD/SCA, NSCD, or NCD. In the subanalysis, in the patients with heart rate <80 and similar heart rates between those who survived and those who experienced SCD/SCA, the patients who died because of SCD or had SCA still had significantly higher TMD-SD compared with patients who survived (Table 2).

TABLE 2 Baseline electrocardiographic parameters

Unlimited HRa	Alive n = 1,377	SCD/SCA n = 66	NSCD n = 71	NCD n = 164
HRa	69 ± 8	71 ± 9 [*]	66 ± 8 [†]	70 ± 9
HRa 12-18	70 ± 9	71 ± 11	66 ± 8 [†]	70 ± 10
SDNN 10	58.5 ± 35.2	70.4 ± 49.7	71.3 ± 49.4	64.9 ± 48.7
QTc	421.9 ± 25.2	438.2 ± 30.6 [‡]	434.0 ± 25.9 [†]	432.2 ± 29.5 [‡]
Average TMD, degrees	28.7 ± 24.6	40.3 ± 26.8 [†]	48.1 ± 28.7 [‡]	35.3 ± 26.6 [*]
QRSTA-SD	4.37 ± 3.51	5.27 ± 4.06	4.23 ± 3.17	4.87 ± 3.64
TW-Ad-SD	3.00 ± 4.15	4.18 ± 4.51	4.96 ± 5.40 [†]	4.05 ± 5.37 [*]
TMD-SD, degrees	2.61 ± 2.55	3.61 ± 2.83 [†]	3.20 ± 2.73	2.64 ± 2.17
HRa <80	Alive n = 1,235	SCD/SCA n = 54	NSCD n = 67	NCD n = 143
HRa	67 ± 7	68 ± 7	65 ± 7 [*]	67 ± 7
HRa 12-18	68 ± 8	68 ± 9	65 ± 8 [†]	68 ± 8
SDNN 10	59.8 ± 34.6	76.9 ± 51.6 [*]	73.0 ± 50.1	68.3 ± 49.4
QTc	421.3 ± 25.1	437.2 ± 32.6 [‡]	433.1 ± 26.2 [†]	430.5 ± 29.3 [†]
Average TMD, degrees	28.7 ± 24.7	39.4 ± 26.3 [†]	47.9 ± 29.2 [‡]	34.7 ± 26.6 [*]
QRSTA-SD	4.36 ± 3.60	4.69 ± 2.89	3.94 ± 2.85	4.80 ± 3.30
TW-Ad-SD	2.99 ± 4.25	3.67 ± 4.06	4.33 ± 4.44 [*]	3.88 ± 4.63
TMD-SD, degrees	2.56 ± 2.55	3.50 ± 2.94 [*]	3.19 ± 2.81	2.65 ± 2.20

Note: Average TMD = 10-min average of T-wave morphology dispersion, which is obtained by calculating the average angle between all possible reconstruction vector pairs of limb leads I-II and chest leads V2-V6 in three-dimensional space and it is expressed in degrees. Spatial heterogeneity due to abnormal repolarization increases this value. HRa = average heart rate during the 10-min period of analysis. HRa 12-18 = average heart rate during the total window between noon and 6 p.m. HRa < 80 = a subanalysis in the patients with heart rate < 80 during the 10-min period of analysis. NCD = non-cardiac death. NSCD = non-sudden cardiac death. QRSTA-SD = standard deviation of QRS-T angle describing temporal variability of the spatial angle between main QRS vector and the main T-wave vector, that is, temporal variability of the spatial angle between the depolarization and repolarization wavefronts. QTc = QT interval corrected for heart rate by the Bazett's formula. SCD = sudden cardiac death. SDNN 10 = average standard deviation of RR interval during the 10-min period of analysis. TMD-SD = standard deviation of T-wave morphology dispersion, which describes temporal variability of TMD, that is, temporal variability of spatial heterogeneity of electrocardiographic repolarization. TW-Ad-SD = standard deviation of T-wave area dispersion, which describes temporal variability of dispersion of T-wave area and shape between the leads I, II, V4-V6, that is, temporal variability of heterogeneity of electrocardiographic repolarization. Please, see Methods section for details.

* $p < .05$,

† $p < .01$,

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

3.2 | Factors associated with sudden cardiac death or sudden cardiac arrest, non-sudden cardiac death, or non-cardiac death after multivariate adjustments

The clinically relevant risk factors of SCD/SCA that remained significant in the univariate comparisons were tested in the Cox multivariate regression analysis. The risk factors that remained significant after adjustments with other covariates were LVEF, type II diabetes, the presence of LBBB, and CCS class (Table 3). These independent predictors of SCD/SCA formed the base of the risk model for SCD/SCA. When the different repolarization parameters were tested in this multivariate clinical risk model, the adjusted TMD-SD was the only variable that retained its significant association with SCD/SCA. TMD-SD did not have significant univariate or multivariate

association with other modes of death. The associations of baseline clinical and electrocardiographic parameters with different modes of death in the Cox regression analysis are shown in Table 3. Heart rate from the analyzed 10-min period did not have significant association with SCD/SCA after relevant adjustments (Table 3). When TMD-SD and heart rate were tested at the same time in the multivariate model, TMD-SD, unlike heart rate, retained its significant predictive power for SCD/SCA (HR 1.105, 95% CIs 1.032-1.183, $p = .004$; HR 1.020, 95% CIs 0.992-1.049, $p = .17$, respectively). When LVEF < median 65%, diabetes, LBBB, and CCS class ≥ 2 , and TMD-SD ≥ 5 were included in the clinical risk model for SCD in this order, the C-index increased as follows: 0.605 (95% CIs 0.547-0.663); 0.674 (95% CIs 0.613-0.736); 0.678 (95% CIs 0.614-0.743); 0.713 (95% CIs 0.659-0.777); 0.722 (95% CIs 0.666-0.791), respectively.

TABLE 3 Univariate and multivariate predictors of sudden cardiac death, non-sudden cardiac death and non-cardiac death

Variable	SCD		NSCD		NCD	
	HR	95% CI	HR	95% CI	HR	95% CI
Age						
uv	1.049	1.016–1.082 [†]	1.149	1.107–1.192 [‡]	1.106	1.082–1.131 [‡]
mv			1.126	1.084–1.170 [‡]	1.103	1.078–1.129 [‡]
Male gender						
uv					1.665	1.154–2.401 [†]
mv					2.735	1.862–4.018 [‡]
DM II						
uv	2.856	1.712–4.765 [‡]	2.515	1.540–4.108 [‡]	1.576	1.159–2.141 [†]
mv	2.439	1.454–4.093 [†]	2.387	1.458–3.908 [†]	1.434	1.044–1.971 [*]
CCS ≥ 2						
uv	2.847	1.715–4.728 [‡]	4.243	2.502–7.193 [‡]	1.721	1.265–2.339 [†]
mv	2.379	1.425–3.972 [†]	2.347	1.358–4.056 [†]		
LBBB						
uv	4.773	2.362–9.643 [‡]	2.969	1.285–6.862 [*]		
mv	2.996	1.391–6.456 [†]				
RBBB						
uv					3.216	2.013–5.138 [‡]
mv					2.230	1.383–3.594 [†]
Anti-t.m.						
uv			0.373	0.136–1.024		
mv						
Diuretics						
uv	1.868	1.152–3.029 [*]	2.984	1.854–4.802 [‡]	2.245	1.653–3.050 [‡]
mv					1.799	1.298–2.495 [‡]
Nitrates						
uv	2.227	1.370–3.621 [†]	2.481	1.542–3.992 [‡]		
mv						
Ca-blocker						
uv			1.730	1.061–2.821 [†]		
mv						
LVEF						
uv	0.950	0.930–0.970 [‡]				
mv	0.967	0.947–0.988 [†]				
LVMI						
uv	1.015	1.007–1.022 [‡]	1.016	1.010–1.023 [‡]		
mv			1.013	1.005–1.020 [†]		
LVEDD						
uv					0.959	0.934–0.985 [†]
mv					0.961	0.936–0.988 [†]
HRa						
uv	1.032	1.003–1.062 [*]	0.958	0.930–0.987 [†]		
mv	1.022	0.993–1.050	0.976	0.948–1.005		
HRa 12–18						
uv			0.951	0.924–0.978 [†]		
mv			0.970	0.943–0.998 [*]		

(Continues)

TABLE 3 (Continued)

Variable	SCD		NSCD		NCD	
	HR	95% CI	HR	95% CI	HR	95% CI
QTc						
uv	1.020	1.012–1.028 [‡]	1.015	1.007–1.024 [‡]	1.013	1.007–1.019 [‡]
mv	1.009	1.000–1.019	1.004	0.995–1.013	1.007	1.000–1.013 [*]
Avg TMD						
uv	1.014	1.006–1.023 [‡]	1.024	1.015–1.032 [‡]	1.008	1.002–1.013 [‡]
mv	1.003	0.993–1.013	1.014	1.005–1.023 [‡]	1.005	0.999–1.011
TW-Ad-SD						
uv			1.024	1.015–1.032 [‡]	1.038	1.012–1.064 [‡]
mv			1.037	0.997–1.079	1.032	1.003–1.062 [*]
TMD-SD						
uv	1.105	1.035–1.180 [‡]				
mv	1.107	1.035–1.185 [‡]				

Abbreviations: CI, confidence interval; HR, hazards ratio; mv, multivariate; uv, univariate. Other abbreviations are the same as in Tables 1 and 2. Only the variables that had a significant difference in univariate comparisons in Tables 1 and 2 were included in the univariate Cox regression analysis. Only the multivariate HRs of clinical variables that remained significant in the multivariate analysis are shown, whereas all the multivariate HRs for electrocardiographic parameters are shown, regardless of being significant or not

* $p < .05$,

[‡] $p < .01$,

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

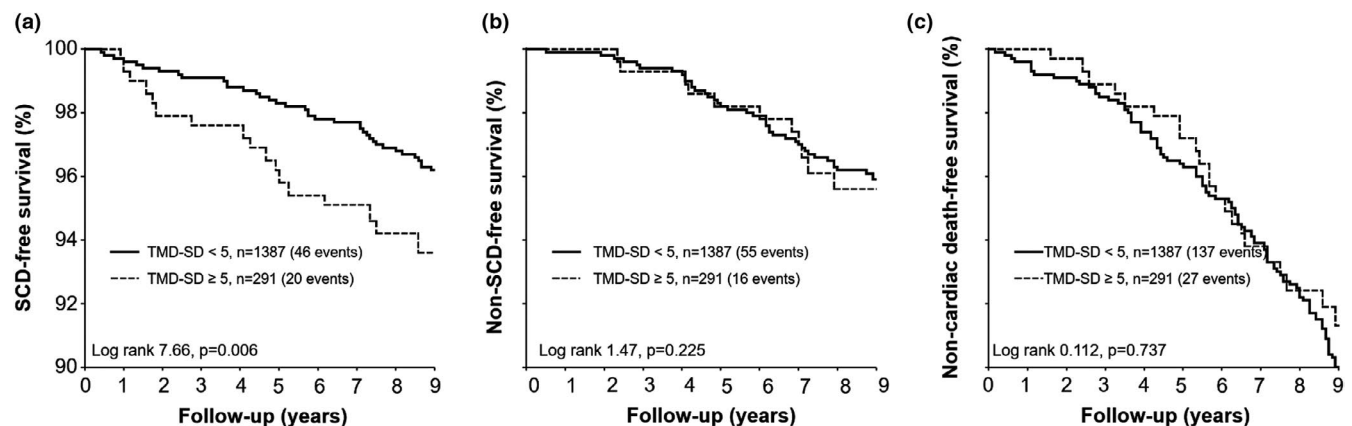


FIGURE 1 Cumulative proportional probability of sudden cardiac death/sudden cardiac arrest-free (a), non-sudden cardiac death-free (b), and non-cardiac death-free (c) survival in patients with the standard deviation of T-wave morphology dispersion (TMD-SD) $<$ or \geq 5. The cutoff point for the Kaplan–Meier survival curves was optimized from the receiver operating characteristics (ROC) curve for sudden cardiac death/sudden cardiac arrest

3.3 | Cumulative proportional probabilities of survival in relation to standard deviation of T-wave morphology dispersion

Figure 1 shows the Kaplan–Meier survival curves depicting the cumulative proportional probabilities of event-free survival for SCD/SCA, NSCD, and NCD in patients classified according to the optimized cutoff point. The cutoff point used in the analyses was obtained from the ROC curve for SCD/SCA.

4 | DISCUSSION

The main finding of the present analysis was that temporal variability of electrocardiographic spatial heterogeneity of repolarization represented by TMD-SD independently predicted the long-time risk of SCD/SCA in a population of CAD patients. In contrast, TMD-SD was not associated with NSCD or NCD even in the univariate model. When the relevant clinical risk indicators were considered in the multivariate analysis, TMD-SD preserved

its predictive power for the risk of SCD. As is seen in Figure 1a, when the optimal cutoff point was determined from the receiver operating characteristics curve, patients with TMD-SD ≥ 5 were at increased risk of SCD. However, in subfigures b and c, the risk for NSCD and NCD was quite similar regardless of TMD-SD value. Our results suggest that TMD-SD could serve as a specific non-invasive risk marker for SCD and equally importantly has predictive power independent of left ventricular functional status, diabetes and other relevant clinical risk indicators in CAD patients who were treated according to modern guidelines and had well-preserved left ventricular function.

Our present findings are in accordance with past discoveries in the field of cardiac repolarization dynamics. In a study with long QT syndrome (LQTS) patients and their unaffected family members, temporal variability of QT interval and of T-wave complexity were shown to be significantly increased in LQTS patients compared with unaffected family members, suggesting that temporal variability of repolarization could predispose the LQTS patients to arrhythmias (Perkiömäki et al., 2002). A more recent study by Kenttä et al. tested the post-exercise dynamics of the spatial QRSTA as a predictor for SCD in 1,297 patients undergoing a clinically indicated exercise stress test and found that attenuated hysteresis of the relation of depolarization and repolarization wavefronts in the post-exercise period was associated with increased risk of cardiac death and SCD (Kenttä et al., 2012). Analysis of a large cohort of 14,024 members of the general population by Waks and colleagues discovered that increased beat-to-beat spatiotemporal variability of the T-wave vector was independently associated with higher risk of SCD, a finding that further constitutes to the growing body of evidence about the role temporal variability of repolarization plays in the process that ultimately manifests as SCD (Waks et al., 2015). We calculated TMD, QRSTA, and TW-Ad on beat-to-beat basis to evaluate the prognostic significance of their temporal variability and found that TMD-SD was most closely associated with risk for SCD.

Despite the still-elusive mechanisms by which spatiotemporal variability of T-wave morphology contributes to increased SCD risk, the individual roles of both spatial and temporal heterogeneity of cardiac repolarization in arrhythmogenesis are well established. Stochastic fluctuations of ion channel activity and gap junction uncoupling have been linked to repolarization abnormalities, after-depolarizations and altered regional conduction velocities, which promote ventricular arrhythmias during acute ischemia (Pueyo et al., 2011). In animal models of myocardial ischemia due to occluded coronary artery, arrhythmias manifest in two distinct phases during the first hours of ischemia, the first phase occurring simultaneously with the reversible stage of myocardial damage and the second phase taking place concurrently with the evolution of the infarction (Di Diego & Antzelevitch, 2011). The precise timing of susceptibility to ischemic ventricular arrhythmias in humans is poorly characterized, but observations suggest a similar biphasic sequence as in the animal models (Clements-Jewery et al., 2005). The vulnerability of myocardium with inhomogeneous repolarization

to ischemia-induced life-threatening ventricular tachyarrhythmias could be one explanation why temporal variability of TMD was specifically associated with SCD and not with NSCD. Another major contributor to cardiac repolarization dynamics is the sympathetic nervous system (SNS), with both clinical and experimental data indicating that increased sympathetic tone can lead to labile myocardial repolarization (Verrier et al., 2009). Recent discovery of SNS-induced periodical low-frequency changes of cardiac repolarization instability and its association with increased risk of cardiovascular mortality could further explain the importance of taking temporal phenomena into account in cardiovascular risk stratification models (Rizas et al., 2017).

There were some limitations in our study. We did not perform repeated electrocardiographic recordings during the follow-up period; instead, the data that contributed to the TMD-SD values were obtained solely from the baseline recordings. Patients with NYHA class IV and planned or existing ICD were excluded from this study, and those patients would likely have had above-average heterogeneity of cardiac repolarization. The number of patients excluded on these grounds was small, however. We outlined the time frame of our analysis to be during the daytime hours, with the second and fourth quarter of the day being left out. Studies have shown that the risk of arrhythmic events is highest in the second and fourth quarter of the day (Singh et al., 2002). Thus, more information on temporal fluctuations of repolarization heterogeneity could be gained from future research acknowledging these circadian characteristics.

In conclusion, the present analysis introduced a novel parameter for assessing temporal variability of spatial heterogeneity of electrocardiographic repolarization, the TMD-SD, which shows close association with the risk of SCD in particular. The appreciation of temporal changes in electrocardiographic spatial heterogeneity of repolarization brings additional information of SCD risk in patients with angiographically verified CAD. The most notable benefit of improved SCD risk stratification would be a better defined subgroup of high-risk individuals among patients that have preserved ejection fraction. After further developments, a refined risk model incorporating temporospatial parameters of cardiac repolarization could hopefully help in selecting targeted therapy, such as ICD, in the future. Our analysis provided further validation to the growing body of evidence about the association between temporospatial electrocardiographic repolarization phenomena and the risk of SCD. However, future studies are needed to confirm our findings and the cutoff point for TMD-SD in predicting SCD needs to be evaluated in independent study populations.

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REFERENCES

- Acar, B., Yi, G., Hnatkova, K., & Malik, M. (1999). Spatial, temporal and wavefront direction characteristics of 12-lead T-wave morphology. *Medical & Biological Engineering & Computing*, *37*, 574–584. <https://doi.org/10.1007/BF02513351>
- Clements-Jewery, H., Hearse, D. J., & Curtis, M. J. (2005). Phase 2 ventricular arrhythmias in acute myocardial infarction: A neglected target for therapeutic antiarrhythmic drug development and for safety pharmacology evaluation. *British Journal of Pharmacology*, *145*, 551–564. <https://doi.org/10.1038/sj.bjp.0706231>
- Deyell, M. W., Krahn, A. D., & Goldberger, J. J. (2015). Sudden cardiac death risk stratification. *Circulation Research*, *116*, 1907–1918. <https://doi.org/10.1161/CIRCRESAHA.116.304493>
- Di Diego, J. M., & Antzelevitch, C. (2011). Ischemic ventricular arrhythmias: Experimental models and their clinical relevance. *Heart Rhythm: The Official Journal of the Heart Rhythm Society*, *8*, 1963–1968. <https://doi.org/10.1016/j.hrthm.2011.06.036>
- Hasan, M. A., & Abbott, D. (2016). A review of beat-to-beat vectorcardiographic (VCG) parameters for analyzing repolarization variability in ECG signals. *Biomedizinische Technik. Biomedical Engineering*, *61*, 3–17. <https://doi.org/10.1515/bmt-2015-0005>
- Junttila, M. J., Kiviniemi, A. M., Lepojärvi, E. S., Tulppo, M., Piira, O.-P., Kenttä, T., Perkiömäki, J. S., Ukkola, O. H., Myerburg, R. J., & Huikuri, H. V. (2018). Type 2 diabetes and coronary artery disease: Preserved ejection fraction and sudden cardiac death. *Heart Rhythm: The Official Journal of the Heart Rhythm Society*, *15*, 1450–1456. <https://doi.org/10.1016/j.hrthm.2018.06.017>
- Kentta, T., Karsikas, M., Junttila, M. J., Perkiomaki, J. S., Seppanen, T., Kiviniemi, A., Nieminen, T., Lehtimäki, T., Nikus, K., Lehtinen, R., Viik, J., Kahonen, M., & Huikuri, H. V. (2011). QRS-T morphology measured from exercise electrocardiogram as a predictor of cardiac mortality. *Europace*, *13*, 701–707. <https://doi.org/10.1093/europace/euq461>
- Kenttä, T. V., Sinner, M. F., Nearing, B. D., Freudling, R., Porthan, K., Tikkanen, J. T., Müller-Nurasyid, M., Schramm, K., Viitasalo, M., Jula, A., Nieminen, M. S., Peters, A., Salomaa, V., Oikarinen, L., Verrier, R. L., Kääh, S., Junttila, M. J., & Huikuri, H. V. (2018). Repolarization heterogeneity measured with T-wave area dispersion in standard 12-lead ECG predicts sudden cardiac death in general population. *Circulation. Arrhythmia and Electrophysiology*, *11*, e005762. <https://doi.org/10.1161/CIRCEP.117.005762>
- Kenttä, T., Viik, J., Karsikas, M., Seppänen, T., Nieminen, T., Lehtimäki, T., Nikus, K., Lehtinen, R., Kähönen, M., & Huikuri, H. V. (2012). Postexercise recovery of the spatial QRS/T angle as a predictor of sudden cardiac death. *Heart Rhythm: The Official Journal of the Heart Rhythm Society*, *9*, 1083–1089. <https://doi.org/10.1016/j.hrthm.2012.02.030>
- Kiviniemi, A. M., Lepojärvi, E. S., Tulppo, M. P., Piira, O.-P., Kenttä, T. V., Perkiömäki, J. S., Ukkola, O. H., Myerburg, R. J., Junttila, M. J., & Huikuri, H. V. (2019). Prediabetes and risk for cardiac death among patients with coronary artery disease: The ARTEMIS study. *Diabetes Care*, *42*, 1319–1325. <https://doi.org/10.2337/dc18-2549>
- Mozaffarian, D., Benjamin, E. J., Go, A. S., Arnett, D. K., Blaha, M. J., Cushman, M., de Ferranti, S., Després, J.-P., Fullerton, H. J., Howard, V. J., Huffman, M. D., Judd, S. E., Kissela, B. M., Lackland, D. T., Lichtman, J. H., Lisabeth, L. D., Liu, S., Mackey, R. H., Matchar, D. B., ... Turner, M. B. (2015). Heart disease and stroke statistics—2015 update: A report from the American Heart Association. *Circulation*, *131*, 29. <https://doi.org/10.1161/CIR.0000000000000152>
- Nearing, B. D., & Verrier, R. L. (2002). Modified moving average analysis of T-wave alternans to predict ventricular fibrillation with high accuracy. *Journal of Applied Physiology*, *92*(2), 541–549. <https://doi.org/10.1152/jappphysiol.00592.2001>
- Perkiömäki, J. S., Zareba, W., Nomura, A., Andrews, M., Kaufman, E. S., & Moss, A. J. (2002). Repolarization dynamics in patients with long QT syndrome. *Journal of Cardiovascular Electrophysiology*, *13*, 651–656. <https://doi.org/10.1046/j.1540-8167.2002.00651.x>
- Pirkola, J. M., Konttinen, M., Kenttä, T. V., Holmström, L. T. A., Junttila, M. J., Ukkola, O. H., Perkiömäki, J. S. (2018). Prognostic value of T-wave morphology parameters in coronary artery disease in current treatment era. *Annals of Noninvasive Electrophysiology*, *23*(4), e12539-<https://doi.org/10.1111/anec.12539>
- Porthan, K., Viitasalo, M., Toivonen, L., Havulinna, A. S., Jula, A., Tikkanen, J. T., Väänänen, H., Nieminen, M. S., Huikuri, H. V., Newton-Cheh, C., Salomaa, V., & Oikarinen, L. (2013). 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. *Circulation. Arrhythmia and Electrophysiology*, *6*, 690–696. <https://doi.org/10.1161/CIRCEP.113.000356>
- Pueyo, E., Corrias, A., Virág, L., Jost, N., Szél, T., Varró, A., Szentandrassy, N., Nánási, P. P., Burrage, K., & Rodríguez, B. (2011). A multiscale investigation of repolarization variability and its role in cardiac arrhythmogenesis. *Biophysical Journal*, *101*, 2892–2902. <https://doi.org/10.1016/j.bpj.2011.09.060>
- Rea, T. D., Pearce, R. M., Raghunathan, T. E., Lemaitre, R. N., Sotoodehnia, N., Jouven, X., & Siscovick, D. S. (2004). Incidence of out-of-hospital cardiac arrest. *The American Journal of Cardiology*, *93*, 1455–1460. <https://doi.org/10.1016/j.amjcard.2004.03.002>
- Rizas, K. D., McNitt, S., Hamm, W., Massberg, S., Kääh, S., Zareba, W., Couderc, J.-P., & Bauer, A. (2017). Prediction of sudden and non-sudden cardiac death in post-infarction patients with reduced left ventricular ejection fraction by periodic repolarization dynamics: MADIT-II substudy. *European Heart Journal*, *38*, 2110–2118. <https://doi.org/10.1093/eurheartj/ehx161>
- Singh, R. B., Kartik, C., Otsuka, K., Pella, D., & Pella, J. (2002). Brain-heart connection and the risk of heart attack. *Biomedicine & Pharmacotherapy*, *56*, 257–265. [https://doi.org/10.1016/S0753-3322\(02\)00300-1](https://doi.org/10.1016/S0753-3322(02)00300-1)
- Smetana, P., Batchvarov, V. N., Hnatkova, K., Camm, A. J., & Malik, M. (2002). Sex differences in repolarization homogeneity and its circadian pattern. *American Journal of Physiology-Heart and Circulatory Physiology*, *282*, 1889–1897. <https://doi.org/10.1152/ajpheart.00962.2001>
- Tereshchenko, L. G., & Feeny, A. (2016). Patient-specific time-varying association between spatial and temporal variability in repolarization and high sensitivity troponin I. *Computing in Cardiology(2010)*, *43*, 333–336.
- Verrier, R. L., & Huikuri, H. (2017). Tracking interlead heterogeneity of R- and T-wave morphology to disclose latent risk for sudden cardiac death. *Heart Rhythm: The Official Journal of the Heart Rhythm Society*, *14*, 1466–1475. <https://doi.org/10.1016/j.hrthm.2017.06.017>
- Verrier, R. L., Kumar, K., & Nearing, B. D. (2009). Basis for sudden cardiac death prediction by T-wave alternans from an integrative physiology perspective. *Heart Rhythm: The Official Journal of the Heart Rhythm Society*, *6*, 416–422. <https://doi.org/10.1016/j.hrthm.2008.11.019>
- Waks, J. W., Soliman, E. Z., Henrikson, C. A., Sotoodehnia, N., Han, L., Agarwal, S. K., Arking, D. E., Siscovick, D. S., Solomon, S. D., Post, W. S., Josephson, M. E., Coresh, J., & Tereshchenko, L. G. (2015). Beat-to-beat spatiotemporal variability in the T vector is associated with sudden cardiac death in participants without left ventricular hypertrophy: The atherosclerosis risk in communities (ARIC) study. *Journal of the American Heart Association*, *4*, e001357. <https://doi.org/10.1161/JAHA.114.001357>
- Yang, H., Bukkapatnam, S. T., & Komanduri, R. (2012). Spatiotemporal representation of cardiac vectorcardiogram (VCG) signals. *Biomedical Engineering Online*, *11*, 16. <https://doi.org/10.1186/1475-925X-11-16>
- Zabel, M., Acar, B., Klingenhöben, T., Franz, M. R., Hohnloser, S. H., & Malik, M. (2000). Analysis of 12-lead T-wave morphology for risk stratification after myocardial infarction. *Circulation*, *102*, 1252–1257. <https://doi.org/10.1161/01.CIR.102.11.1252>

- Zabel, M., Malik, M., Hnatkova, K., Papademetriou, V., Pittaras, A., Fletcher, R. D., & Franz, M. R. (2002). Analysis of T-wave morphology from the 12-lead electrocardiogram for prediction of long-term prognosis in male US veterans. *Circulation*, *105*, 1066-1070. <https://doi.org/10.1161/hc0902.104598>
- Zipes, D. P., & Wellens, H. J. (1998). Sudden cardiac death. *Circulation*, *98*, 2334-2351. <https://doi.org/10.1161/01.CIR.98.21.2334>

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