Prognostic significance of flat T-waves in the lateral leads in general population

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Short title:

The significance of flat T-waves

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Conflict of Interest

None

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Abstract

Background

Negative T-waves are associated with sudden cardiac death (SCD) risk in the general population. Whether flat T-waves also predict SCD is not known. The aim of the study was to examine the clinical characteristics and risk of SCD in general population subjects with flat T-waves.

Methods

We examined the electrocardiograms of 6750 Finnish general population adults aged ≥30 years and classified the subjects into 3 groups: 1) negative T-waves with an amplitude ≥0.1 mV in ≥2 of the leads I, II, aVL, V4–V6, 2) negative or positive low amplitude T-waves with an amplitude <0.1 mV and the ratio of T-wave and R-wave <10% in ≥2 of the leads I, II, aVL, V4–V6, and 3) normal positive T-waves (not meeting the aforesaid criteria). The association between T-wave classification and SCD was assessed during a 10-year follow-up.

Results

A total of 215 (3.2%) subjects had negative T-waves, 856 (12.7%) flat T-waves, and 5679 (84.1%) normal T-waves. Flat T-wave subjects were older and had more often cardiovascular morbidities compared to normal T-wave subjects, while negative T-wave subjects were the oldest and had most often cardiovascular morbidities. After adjusting for multiple factors, both flat T-waves (hazard ratio [HR] 1.81; 95% confidence interval [CI] 1.13–2.91) and negative T-waves (HR 3.27; 95% CI 1.85–5.78) associated with SCD.

Conclusions

Cardiovascular risk factors and disease are common among subjects with flat T-waves, but these minor T-wave abnormalities are also independently associated with increased SCD risk.

Introduction

The T-wave in the electrocardiogram (ECG) coincides with the repolarization of the ventricles. Numerous physiological and pathological factors, e.g. age, sex, autonomic tone, drugs, and the presence of a cardiac disease, may affect the T-wave morphology, and T-wave abnormalities can be used as diagnostic tools in certain acute and chronic cardiac conditions [1]. There has been also growing interest on the long-term prognostic significance of T-wave changes, as there is an ongoing search for novel inexpensive and large-scale applicable prediction tools for sudden cardiac death (SCD). Several T-wave abnormalities, with varying complexity and applicability to clinical practice, have been associated with increased risk of SCD. Negative T-waves are easy to notice in clinical practice and are shown to predict SCD [2]. Other relatively simple T-wave abnormalities associated with SCD risk include wide frontal QRS-T angle and prolonged Tpeak-to-Tend interval [3–5]. On the other hand, more complex T-wave risk markers, including T-wave alternans, repolarization heterogeneity markers, and three-dimensional T-wave parameters usually require special computer analysis [5–8]. T-waves with low amplitude are easily assessed from the ECG, and they have been associated with cardiovascular mortality in the general population [9–11]. However, whether these flat T-waves are also linked to SCD risk in the general population is not known. Therefore, we investigated the characteristics of flat T-waves in a large Finnish general population cohort, and assessed the risk for SCD associated with these T-wave abnormalities.

Methods

Study population

The study population consisted of 7217 participants of the Social Insurance Institution's Mini-Finland Health Survey conducted in 1978–1980. Participants were aged ≥30 years and the survey population was a representative sample of the Finnish population. Participants were interviewed regarding their health status, medications, diseases, symptoms, and lifestyle. Furthermore, participants underwent health examinations including measurements of blood pressure, body mass index (BMI), and total serum cholesterol, in addition to the recording of an ECG. Moreover, plasma potassium levels were measured from a prespecified subset of participants. Participants' baseline diagnoses were assessed using structured criteria based on the interviews and the health examination findings (Supplemental Methods). The Mini-Finland Health Survey methods have been reported more extensively previously [12].

All participants of the Mini-Finland Health Survey were fully informed about the study, they participated in the study voluntarily, and the use of information for medical research was explained to them. Agreeing to participate in the baseline health examination was taken to indicate informed consent. The participants were free to unconditionally withdraw their consent at any time, in which case their data were deleted. The study was carried out following ethical guidelines and principals of the Declaration of Helsinki. The study protocol and the practice of the subjects' voluntary participation indicating informed consent were approved by the Institutional Review Board (IRB) of National Institute for Health and Welfare (IRB 00007085, Federalwide Assurance (FWA) 00014588).

Electrocardiographic measurement and analyses

A standard 12-lead ECG with a paper speed of 50 mm/s and calibration of 1 mV/10 mm was recorded from all study participants during the health examination in 1978–1980. After a few months, a second ECG was recorded from a subgroup of participants who had signs of cardiovascular disease in the health examinations, which were separately evaluated to assess the permanence of flat T-waves as an ECG finding over time. The recorded paper ECGs were digitized and digitally assessed in 2015–2016. Digital analysis was conducted by three examiners with a custom-made ECG analysis software. Using median beats, T-wave amplitude was assessed digitally with respect to the true baseline with 0.01 mV accuracy from each lead. The paper ECG digitizing and digital assessment method has been described in more detail previously [13]. After excluding subjects with missing health examination data, subjects with missing or unreadable ECGs, and subjects with atrial fibrillation, atrial flutter, left or right bundle branch block, second or third-degree atrioventricular block, pre-excitation pattern, pacemaker rhythm, or ECG findings not representing the general population, a total of 6750 subjects remained for the analyses.

Subjects were classified into 3 groups according to the T-wave polarities and amplitudes in leads I, II, aVL, V4–V6: 1) negative T-waves (negative T-wave with an amplitude of ≥0.1 mV in ≥2 of the leads), 2) flat T-waves (positive or negative T-wave with and amplitude <0.1 mV and the ratio of T-wave and R-wave <10% in ≥2 of the leads and not meeting the criterion for negative T-waves group), and 3) normal T-waves (not meeting the criteria for negative T-waves or flat T-waves groups).

QRS duration, QT interval and Tpeak-to-Tend interval were measured from lead V5. Bazett's formula was used for QT interval correction for heart rate. Frontal QRS axis and T axis were calculated automatically by the digital measurement software. QTc >450 ms in men and >460 ms in women, QRS-T angle >90 °, and Tpeak-to-Tend >90 ms were used as

cut-offs for abnormal values when the parameters were used as dichotomous categorical variables. ST-segment depressions were defined as negative ST-segments of ≥0.1 mV at 60 ms from the J point in ≥2 of the leads I, II, III, aVL, aVF, and V1–V6.

Follow-up

Survey participants were followed from the baseline examination in 1978–1980 until the end of 2011 using the nation wide Causes of Death Register maintained by Statistics Finland. During the complete follow-up time of the Mini-Finland Health Survey, 1077 subjects (27% of all deceased) of all the Mini-Finland participants were autopsied, of which 194 were SCD cases (48% of SCD cases). SCD cases were determined by 2 cardiologists based on the death certificates, hospital records, and autopsy records using the modified Cardiac Arrhythmia Suppression Trial (CAST) criteria [14]. In cases of disagreement, a third cardiologist reviewed the case and made the final classification. The primary endpoint was SCD, and the secondary endpoints were cardiac death and death from any cause. Follow-up time was limited to 10 years in the primary analyses, as the cardiovascular risk profile could change during a longer follow-up. The complete follow-up time of the Mini-Finland Health Survey was used in the secondary analyses.

Statistical analysis

Age and sex adjusted mean values ± standard deviation for continuous variables and the prevalence of categorical variables were compared using the general linear model. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using the Cox proportional hazards model. The multivariate models were adjusted with age, sex, systolic blood pressure, heart rate, total serum cholesterol, BMI, diabetes, active smoking, beta blocker medication,

left ventricular hypertrophy (LVH) on ECG based on the Sokolow-Lyon criterion, and presence of cardiac disease. The survival of subjects in T-wave groups was compared using Kaplan–Meier plots. The statistical significances of effect modification by baseline characteristics were tested using the Wald test by entering an interaction term of T-wave class and the respective baseline characteristic. All reported p-values are two-sided and $p<0.05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics (version 25).

Results

A total of 215 (3.2%) subjects presented with negative T-waves, 856 (12.7%) with flat T-waves, and 5679 (84.1%) with normal upright T-waves. Examples of different T-wave morphologies are demonstrated in Figure 1. The distribution of T-wave morphologies in individual leads is presented in the Supplemental Figure.

The baseline characteristics of the subjects with different T-wave morphologies are displayed in Table 1. The age distributions of subjects with normal, flat, and negative T-waves are displayed in the Supplemental Table 1. Subjects with flat or negative T-waves were older, had higher blood pressure and heart rate, and had more often diabetes and cardiac morbidities ($p<0.05$ for all) than subjects with normal T-waves. However, subjects with negative T-waves had higher systolic blood pressure and had more often cardiac disease, coronary artery disease (CAD), diabetes, and beta blocker medication compared to subjects with flat T-waves ($p<0.05$ for all). Serum potassium was measured from a prespecified group of 2798 subjects (mean 4.5±0.4 mmol/l), with no significant differences between the T-wave groups.

The baseline ECG features are shown in Table 2. QRS and Tpeak-to-Tend intervals were longer in subjects with negative T-waves than subjects with either normal or flat T-waves ($p<0.05$ for both). LVH and ST-segment depressions were most common among negative T-wave subjects while being more common among flat T-wave subjects than normal T-wave subjects ($p<0.05$ for all). The frontal QRS-T angle was narrowest among normal T-wave subjects and widest in negative T-wave subjects ($p<0.05$). QTc was longest in subjects with flat T-waves and shortest in subjects with negative T-waves ($p<0.05$).

A second ECG was recorded few months after the baseline examinations from 247 subjects with flat T-waves (28.9% of the subjects with flat T-waves). Flat T-waves were

again observed in 149 (60.3%) of the subjects, while 24 subjects (9.7%) had negative T-waves, and 3 (1.2%) subjects had LBBB in the repeat ECG.

During the 10-year follow up, 131 subjects (60.9%) with negative T-waves, 267 subjects (31.2%) with flat T-waves, and 547 subjects (9.6%) with normal T-waves died. Of these, 25 (19.1%) in negative T-wave subjects, 32 (12.0 %) in flat T-wave subjects, and 60 (11.0%) in normal T-wave subjects were SCDs. The survival curves for SCD and all-cause mortality according to the T-wave group are presented in Figure 2. Both flat T-waves and negative T-waves associated with SCD, cardiac death, and all-cause mortality when compared to subjects with normal T-waves. Subjects with negative T-waves had worse prognosis compared to subjects with flat T-waves. After multiple adjustments, flat T-waves subjects had HR 1.81 (95% CI 1.13–2.91) and negative T-wave subjects had HR 3.27 (95% CI 1.85–5.78) for SCD, compared to subjects with normal T-waves. The prognoses associated with individual T-wave abnormalities are displayed in Table 3.

No significant effect modification was found between T-wave class and sex, age ≤50 or >50 years, BMI ≤25 or >25 kg/m^2, heart rate ≤70 or >70 bpm, presence of LVH, presence of hypertension diagnosis, or presence of cardiac disease diagnosis for SCD risk.

When ECG repolarization parameters wide QRS-T angle, prolonged QTc, and prolonged Tpeak-to-Tend interval were used as dichotomous categorical variables and entered simultaneously with ST-segment depressions and T-wave class into an age and sex adjusted model, only ST-segment depressions and T-wave class associated with increased SCD risk, with both flat T-waves and negative T-waves associating with risk of SCD (Supplemental Table 2). When further adjusted with multiple factors, only T-wave class associated with SCD risk, with both flat T-waves and negative T-waves remaining associated with risk of SCD ($p<0.05$).

In the secondary analyses using the complete follow-up of the Mini-Finland Health Survey (mean 24.5±10.3 years), flat T-waves and negative T-waves similarly associated with all endpoints, albeit not as strongly as in the primary analyses. During the complete follow-up, flat T-waves had HR 1.40 (95% CI 1.05–1.85) for SCD when compared to normal T-wave subjects after multivariate adjustments. The risks of endpoints associated flat T-waves and negative T-waves during the complete follow-up are presented in the Supplemental Table 3.

Discussion

In this large, prospective study, subjects with flat T-waves were more likely to have cardiovascular risk factors and cardiac disease compared to subjects with normal T-waves. Furthermore, flat T-waves independently associated with increased risk of SCD, in addition to cardiac death, and death from any cause. Still, cardiovascular morbidities were most common and the prognosis poorest among subjects with negative T-waves.

Normally, T-waves are upright in most of the ECG leads, and negative T-waves in leads I, II, V3–V6 are considered abnormal [1]. Multiple factors can have an effect on T-waves polarity and amplitude, for example age, sex, heart rate, autonomic nervous system, electrolyte disturbances, and drugs [1]. Furthermore, T-wave changes have been associated with cardiovascular conditions, e.g. hypertension, acute and chronic manifestations of CAD, left ventricular hypertrophy, and cardiomyopathies [1].

Since the T-wave corresponds to the vulnerable repolarization period of the cardiac cycle, multiple T-wave parameters have been studied and linked with increased risk for arrhythmic death. T-wave inversions, abnormal T-wave axis, and wide QRS-T angle have been associated with SCD in the general population [2,3,5]. Furthermore, prolonged Tpeak-to-Tend interval has been associated with SCD risk in the general population, although not all studies have had similar findings [4,5]. In addition, several complex T-wave parameters, including T-wave alternans, repolarization heterogeneity markers, and spatial T-wave parameters, have been shown to associate with increased SCD risk, but efficient analysis of these parameters requires special computer software [5–8].

Low amplitude or flat T-waves have been associated with sudden cardiac arrest in subjects with hypertrophic cardiomyopathy [15], and they are also more prevalent among subjects with early repolarization who will suffer ventricular fibrillation, compared to subjects with early repolarization with benign prognosis [16]. Low amplitude T-waves have been

241 linked also to ventricular tachycardia and ventricular fibrillation risk in some patients with
242 implantable cardioverter defibrillator [17]. Moreover, when flat T-waves were classified
243 together with negative T-waves in middle-aged men, this group of subjects was at increased
244 risk for SCD, compared to subjects with normal positive T-waves [18]. The present study is
245 the first to demonstrate that flat T-waves independently associate with increased SCD risk in
246 the general population.

247 After relevant exclusions, the prevalence of flat T-waves was 13% in the Mini-
248 Finland Health Survey cohort of the present study. The definition used in the present study
249 included both negative and positive T-waves with an amplitude <0.1 mV and the ratio of T-
250 wave and R-wave <10% as flat T-waves. The amplitude cut-off of ≥0.1 mV has been
251 commonly used for negative T-waves, as more minor negative T-waves can be difficult to be
252 definitely determined as negative in comparison to isoelectric or low amplitude biphasic or
253 positive T-wave [1,2]. Previous studies have commonly used the Minnesota Code definitions
254 to assess minor T-wave abnormalities, with prevalences ranging from 2% to 13% [9–11].
255 Although there are small differences between the definitions used in the present and the
256 previous studies, flat T-waves seem to be a relatively common finding in the general
257 population.

258 In the present study, abnormal T-waves were more prevalent among older
259 subjects. However, no significant effect modification was noted between the T-wave class and
260 age group, suggesting that age does not affect the prognosis associated with abnormal T-
261 waves. Subjects with flat T-waves also had more often cardiovascular morbidities than
262 subjects with normal T-waves. Nonetheless, flat T-waves predicted SCD, cardiac mortality
263 and all-cause mortality also independently from cardiovascular risk factors and diseases.
264 Furthermore, no significant effect modification between the T-wave class and presence of

diagnosed cardiac disease was observed. Finally, negative T-wave subjects had the highest prevalence of cardiovascular morbidities and even worse prognosis.

T-wave morphology changes are caused by local or diffuse voltage gradient and spatial changes in the ventricular repolarization [1]. T-wave changes after myocardial infarction are assumed to be caused by nonradial potential gradients or decreased transmural conduction velocity [19]. Other plausible mechanisms causing T-wave changes in heart diseases include alterations in the autonomic nervous system and ventricular myocyte hypertrophy [1]. Accordingly, it could be speculated that flat T-waves may in some cases act as markers of underlying electrical or structural cardiac pathology, that may be less severe than in subjects with negative T-waves. Moreover, myocardial fibrosis is also associated with T-wave inversion and T-wave changes among SCD victims, especially in subjects with ischemic heart disease [20]. Non-specific ST-T abnormalities have been also linked to impaired left ventricular relaxation causing abnormal repolarization, with cardiac fibrosis being a possible underlying mechanism [21]. Consequently, flat T-waves could also be a direct sign of increased vulnerability for fatal ventricular arrhythmias.

We compared the T-wave classification to other easily assessable ECG repolarization markers that have been associated with SCD. Some of the other analyzed markers have independent clinical value, e.g. ST-segment depression may indicate an underlying CAD. ST-segment depressions were most common in subjects with negative T-waves, but were rarely observed in subjects with normal T-waves. This was in concordance with the prevalence of CAD diagnosis in the health examinations, with the highest prevalence of CAD observed in subjects with negative and lowest prevalence in subjects with normal T-waves. Prolonged QTc, a known marker of increased risk of SCD, was notably longer among subjects with flat T-waves. Flat T-waves are known to decrease the certainty of determining the end of T-wave, which may explain the longer QT intervals [22]. Nonetheless, when the

repolarization markers were analyzed simultaneously in a multivariate model, the T-wave classification was the only one that remained associated with SCD risk. This could indicate, that the simple analysis of the polarities and amplitudes of the T-waves could relay major information about the association between repolarization and SCD risk in clinical practice.

Limitations

Due to the inclusion criterion of age ≥30 years, these findings may not be directly applicable to younger adult populations. As a further limitation, although the baseline examinations were extensive, an echocardiographic study was not performed to survey participants, and, consequently, no data was available on the cardiac structure or systolic function of the heart. Moreover, although flat T-waves were a stable finding in the majority of the cases, in some cases flat T-waves seems to be observable only in some of the ECG recordings. Finally, the results may not be directly applicable to modern populations, as diagnostic tests and treatments of cardiovascular disease have improved since the baseline examinations of the Mini-Finland Health Survey in 1978–1980. However, this limitation is inevitable in this kind of cohort studies with long follow-up periods.

Conclusions

Flat T-waves are a relatively common finding in the general population, but they are often a sign of underlying cardiac disease. Furthermore, flat T-waves are independently associated with increased SCD risk, although the prognosis is better than observed with negative T-waves. More focus should be placed on these minor T-wave abnormalities in the future, as individuals with these ECG patterns may benefit from a careful clinical evaluation and closer monitoring.

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Figure legends

Figure 1 legend

Demonstration of different T-wave morphologies. A) A normal T-wave, B) a flat T-wave, and C) a negative T-wave.

Figure 2

Figure 2 legend

Survival curves for A) SCD and B) all-cause mortality according to the T-wave morphology. The Y-axis of A) graph is scale broken to better illustrate the SCD survival curves. Survival curves were compared with Logrank test.

SCD = sudden cardiac death.

Tables

Table 1

Baseline characteristics

	Normal T-waves n=5679 (84.1%)	Flat T-waves n=856 (12.7%)	Negative T-waves n=215 (3.2%)	Flat vs normal T-waves p-value	Negative vs normal T-waves p-value	Flat vs negative T-waves p-value
Male sex (%) †	2656 (46.8%)	312 (37.5%)	84 (39.1%)	0.002	ns	ns
Age (yr) ‡	48.9±13.0	60.6±12.8	68.4±10.5	<0.001	<0.001	<0.001
Systolic blood pressure (mmHg) §	140±21	156±25	167±29	<0.001	<0.001	0.02
Diastolic blood pressure (mmHg) §	86±11	91±12	90±13	<0.001	0.03	ns
Hypertension (%) §	2995 (52.7%)	698 (81.5%)	204 (94.9%)	<0.001	<0.001	ns
Heart rate (bpm) §	67±13	73±15	72±14	<0.01	0.01	ns
Total serum cholesterol (mmol/l) §	6.9±1.4	7.3±1.4	7.4±1.6	ns	ns	ns
Body mass index (kg/m^2) §	25.6±3.9	27.7±4.7	26.6±4.3	<0.001	ns	<0.001
Cardiac disease (%) §	635 (11.2%)	341 (39.8%)	174 (80.9%)	<0.001	<0.001	<0.001
Coronary artery disease (%) §	380 (6.7%)	219 (25.6%)	103 (47.9%)	<0.001	<0.001	<0.001
Diabetes (%) §	164 (2.9%)	128 (15.0%)	60 (27.9%)	<0.001	<0.001	<0.001
Smoking (%) §	1348 (23.7%)	145 (16.9%)	36 (16.7%)	ns	ns	ns
β-blocker medication (%) §	305 (5.4%)	93 (10.9%)	50 (23.3%)	<0.001	<0.001	<0.001

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415 Continuous variables are presented as mean values ± standard deviation and categorical variables as prevalences. Hypertension = systolic blood

416 pressure >140mmHg, diastolic blood pressure >90, or diuretic, beta-blocker or other hypertensive drug therapy.

417 Between group comparisons were: † adjusted for age, ‡ adjusted for sex, and § adjusted for age and sex.

418

419 *Table 2*

420 Electrocardiographic features

	Normal T-waves n=5679 (84.1%)	Flat T-waves n=856 (12.7%)	Negative T-waves n=215 (3.2%)	Flat vs normal T-waves p-value	Negative vs normal T-waves p-value	Flat vs negative T-waves p-value
QRS duration (ms)	84±11	84±12	88±15	ns	<0.001	<0.001
QTc (ms)	406±25	428±39	392±41	<0.001	<0.001	<0.001
LVH (%)	681 (12.0%)	147 (17.1%)	100 (46.8%)	0.006	<0.001	<0.001
Frontal QRS axis (degrees)	29±39	11±36	11±38	<0.001	ns	0.05
Frontal T-wave axis (degrees)	24±25	15±75	1±136	<0.001	<0.001	<0.001
Frontal QRS-T angle (degrees)	34±28	73±48	140±36	<0.001	<0.001	<0.001
Tpeak-to-Tend (ms)	80±13	71±22	86±34	<0.001	<0.001	<0.001
ST-segment depressions (%)	105	103 (12.0%)	104	<0.001	<0.001	<0.001

	(1.8%)	(48.4%)

Continuous variables are presented as mean values ± standard deviation and categorical variables as prevalences. Ns = not significant. LVH = Left ventricular hypertrophy based on Sokolow-Lyon ECG criterion. QRS duration, QTc, and Tpeak-to-Tend were assessed from lead V5. ST-segment depressions = negative ST-segment of ≥0.1 mV at 60 ms from the J point in ≥2 of the following leads: I, II, III, aVL, aVF, and V1–V6. Between group comparisons were adjusted for age and sex.

Table 3

Prognostic significance of flat T-waves and negative T-waves during the 10-year follow-up

	Normal T-waves	Flat T-waves		Negative T-waves	
	n=5679 (84.1%)	n=856 (12.7%)	p-value	n=215 (3.2%)	p-value
SCD					
No. of SCDs (% of subjects)	60 (1.0%)	32 (3.7%)		25 (11.6%)	
Age and sex adjusted HR (95% CI)	1	2.55 (1.62−4.00)	<0.001	6.50 (3.87−10.91)	<0.001
Multivariate adjusted HR (95% CI)	1	1.81 (1.13−2.91)	0.014	3.27 (1.85−5.78)	<0.001
Cardiac death					
No. of cardiac deaths (% of subjects)	194 (3.4%)	116 (13.6%)		79 (36.7%)	
Age and sex adjusted HR (95% CI)	1	2.25 (1.78−2.86)	<0.001	4.51 (3.40−5.98)	<0.001

Multivariate adjusted HR (95% CI)	1	1.57 (1.22−2.02)	<0.001	2.29 (1.68−3.11)	<0.001
Death from any cause						
No. of deaths (% of subjects)	547 (9.6%)	267 (31.2%)		131 (60.9%)	
Age and sex adjusted HR (95% CI)	1	1.87 (1.61−2.18)	<0.001	2.79 (2.28−3.41)	<0.001
Multivariate adjusted HR (95% CI)	1	1.54 (1.31−1.80)	<0.001	1.85 (1.48−2.30)	<0.001

429

430 M

431 u

432 l

433 t

434 i

435 v

436 a

437 r

438 i

439 a