T-wave alternans predicts mortality in a population undergoing a clinically indicated exercise test

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Introduction

The merits of a clinical exercise test as a prognostic means are well recognized. Exercise capacity,¹ levels and changes of blood pressure,² as well as heart rate (HR) profile³ and certain electrocardiographic (ECG) parameters¹ have been shown to predict all-cause and cardiac mortality. T-wave alternans (TWA) is a relatively novel ECG index representing beat-to-beat alternation in the shape, amplitude, or timing of the ST-segment and the T-wave. The main contemporary use of TWA is based on the spectral analysis of microvolt-level T-wave amplitude during exercise. TWA is considered to represent spatial⁴ or temporal⁵ variations in ventricular repolarization, and it has been linked to both inducible and spontaneous ventricular tachyrhythmias as well as to the mechanisms leading to their initiation.⁶

Keywords

Arrhythmia; Electrocardiography; Exercise; Mortality; Tachyarrhythmia

Aims As a part of the Finnish Cardiovascular Study, we tested the hypothesis that T-wave alternans (TWA) predicts mortality in a general population of patients referred for a clinical exercise test.

Methods and results A total of 1037 consecutive patients (mean age ± SD of 58 ± 13 years, 673 men and 364 women) with a clinically indicated exercise test and with technically successful electrocardiographic (ECG) data during a bicycle ergometer test were included in the study. Digital ECGs were recorded and TWA was analysed continuously with the time-domain modified moving average method. The maximum TWA value at heart rate (HR) < 125 b.p.m. was derived and its capacity to stratify risk for all-cause death, cardiovascular death, and sudden cardiac death (SCD) was tested. During a follow-up of 44 ± 7 months (mean ± SD), 59 patients died; 34 were due to cardiovascular causes and 20 were due to SCD. In multivariate analysis after adjustment for age, sex, use of β-blockers, functional class, maximal HR during exercise, previous myocardial infarction, and other common coronary risk factors, the relative risk of TWA/C⁶ for SCD was 7.4 (95% CI, 2.8–19.4; P < 0.001), for cardiovascular mortality 6.0 (95% CI, 2.8–12.8; P < 0.001), and for all-cause mortality 3.3 (95% CI, 1.8–6.3; P = 0.001).

Conclusion Time-domain TWA analysis powerfully predicts mortality in a general population undergoing a clinical exercise test.

The accuracy and usefulness of exercise-induced TWA in predicting arrhythmic events and death have been investigated in several studies⁷ with, however, relatively small numbers of participants,⁸–²⁰ with exception of two larger studies.²¹,²² These studies have mostly included patients with a high risk of life-threatening arrhythmias,⁷ such as those with a documented near-fatal arrhythmic event, impaired left ventricular function,¹⁰,¹²,¹⁹ congestive heart failure,⁸,¹³–¹⁵,¹⁷,¹⁸ ischaemic cardiomyopathy,²² or lower risk patients with prior MI.⁹,²⁰,²¹ Surprisingly, despite a decade of research, there have been no studies of the prognostic significance of TWA in more general populations undergoing routine exercise testing. This gap in our knowledge may be attributable to the inherent restrictions of the spectral approach, which, because of data stationarity, dictates the use of a non-standard exercise test to elevate and fix HR for a sustained period and requires specialized electrodes. To circumvent these difficulties, we employed...
the time-domain modified moving average (MMA) analysis of TWA. The method has undergone extensive testing in the laboratory and has been shown in smaller studies with post-MI, implantable cardioverter defibrillator patients, and in those at increased risk for impending ventricular tachyarrhythmias to be capable of detecting increased cardiac electrical instability and risk for arrhythmia. The present study was designed to test the hypothesis that TWA has prognostic power in a more general population undergoing a clinically indicated exercise test as a part of the Finnish Cardiovascular Study (FINCAVAS).

Methods

Study cohort

As described in the detailed study protocol of FINCAVAS, all consecutive patients undergoing exercise stress test at Tampere University Hospital between October 2001 and January 2003 and willing to participate in the study were recruited. A total of 1037 patients (673 men and 364 women) with technically successful exercise tests (96.6% of all the tests) were included in the study (Tables 1 and 2). A test was technically adequate if storing the haemodynamic data and continuous digital ECG signal was successful. Patients with atrial fibrillation were not excluded, as this condition does not hinder TWA assessment by the MMA method.

The main indications for the exercise test were diagnosis of coronary heart disease (CHD, frequency 46%), testing vulnerability to arrhythmia during exercise (18%), and evaluation of work capacity (19%) and adequacy of the CHD treatment (24%), as well as obtaining an exercise test profile prior to an invasive operation (13%) or after an MI (10%); some patients had more than one indication. The study protocol was approved by the Ethics Committee of the Tampere University Hospital District, Finland, and all patients gave informed consent prior to the interview and measurements as stipulated in the Declaration of Helsinki.

Study flow

After an informed consent was signed, the medical history of each patient was collected with a computer-based questionnaire form. Thereafter, the exercise test was performed.

Exercise test protocol

Prior to the routine exercise stress test, the subject lay down in the supine position for 10 min, and the resting ECG was digitally recorded. The upright exercise test was performed using a bicycle ergometer with electrical brakes. The lead system used was the Mason–Likar modification of the standard 12-lead system. The initial workload varied from 20 to 30 W, and the load was increased stepwise by 10-30 W every minute. Continuous ECGs were digitally recorded at 500 Hz with CardioSoft exercise ECG system (Version 4.14, GE Healthcare, Freiburg, Germany) and analysed fully automatically by the GE Healthcare-released version of the MMA method.

During the test, HR was continuously registered with ECG, while systolic arterial pressure and diastolic arterial pressure were measured with a brachial cuff every 2 min.

Table 1 Patient characteristics for all participants according to T-wave alternans 65 μV cut point

<table>
<thead>
<tr>
<th></th>
<th>TWA &lt; 65 μV (n = 950)</th>
<th>TWA ≥ 65 μV (n = 87)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean SD</td>
<td>Mean SD</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>58 ± 13</td>
<td>60 ± 12</td>
<td>0.24</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>27.3 ± 4.6</td>
<td>27.4 ± 4.9</td>
<td>0.86</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171 ± 9</td>
<td>172 ± 8</td>
<td>0.16</td>
</tr>
<tr>
<td>HR at rest (b.p.m.)</td>
<td>63 ± 12</td>
<td>64 ± 12</td>
<td>0.40</td>
</tr>
<tr>
<td>SAP at rest (mmHg)</td>
<td>135 ± 19</td>
<td>137 ± 22</td>
<td>0.39</td>
</tr>
<tr>
<td>Reached HR of expected maximum (%)</td>
<td>76 ± 15</td>
<td>74 ± 14</td>
<td>0.28</td>
</tr>
</tbody>
</table>

The P-values are from the t-test for independent samples. BMI, body-mass index; HR, heart rate; SAP, systolic arterial pressure.

Measurement of T-wave alternans

Assessing the relationship between TWA and mortality is one of the original goals of FINCAVAS. The algorithm used in the identification and quantification of TWA is based on the time-domain MMA analysis that has been described in detail earlier. In brief, the MMA algorithm separates odd from even beats. Average morphologies of both the odd and even beats are calculated separately and continuously updated by a weighting factor of 1/8 or 1/32 of the difference between the ongoing average and the new incoming beats. The update is calculated for every incoming beat and results in continual moving averages of the odd and even beats. This approach is intrinsically robust and makes MMA suitable for TWA analysis during the period of activity or fluctuating HRs. In addition, algorithms have been incorporated to reduce the influence of noise and artefacts, such as those caused by pedalling and respiration.

The TWA values were calculated continuously during the entire exercise test from rest to recovery using all standard leads (I, II, III, aVR, aVL, aVF, and V1-V6). The maximum TWA value at HR < 125 b.p.m. was derived. TWA values at higher HR were excluded, based on the previous results indicating that inaccuracies in TWA measurement can result at HR exceeding this range.

The TWA values derived by the MMA method are larger by a factor of ~4–6 than the values reported by the spectral method. This difference is attributable to the fact that the time-domain MMA method determines the maximum difference in the T-wave amplitude between successive beats, while the spectral method derives an average value from its spectra, which are generated across the entire T wave and across 128 beats.
Ejection fraction

Measurement of ejection fraction (EF) is not routine for patients referred for a clinical exercise test. However, EF was determined for 529 (51%) of the study patients with echocardiography (n = 522) or isotope techniques (n = 7) within 6 months (average, 43 days) of the exercise test.

Follow-up

Death certificates were received from the Causes of Death Register, maintained by Statistics Finland, in January 2006; this source has been shown to be reliable. The certificates included causes of death based on the 10th revision of the International Classification of Diseases (ICD-10). The diagnosis numbers and certificate texts were used to classify the deaths as all-cause, cardiovascular death, and sudden cardiac death (SCD; defined as a cardiac death within 24 h after the onset of symptoms).

Statistical analysis

The analyses were performed for two different incremental update factors of the TWA detection algorithm: 1/32 and 1/8, the latter of which proved to be superior in the prediction of death, consistent with experimental and clinical studies. Several cut points were evaluated, including the value coinciding with the 75th percentile (46 μV), the cut point that proved to predict cardiac arrest or arrhythmic death in a prior study. In addition, the cut points of 46 (75th percentile) and 65 μV (93rd percentile, which yielded the best Cox regression results) were used in subsequent analyses. The MMA algorithm was not tuned to the data.

Follow-up

During the follow-up period of 44 ± 7 months (mean ± SD), there were 59 deaths (5.7% of the population). Of those, 34 (3.3%) were classified as cardiovascular death and 20 (1.9%) further as SCD. The causes of death for four (0.4%) patients remained unknown. Patient characteristics and number of deaths for those with TWA < 65 μV (n = 950) and TWA ≥ 65 μV (n = 87) are given in Tables 1 and 2. EF for 529 patients was 65 ± 15% (mean ± SD). Only 67 patients (12.7%) had EF < 50%, and only eight patients (1.5%) presented with EF < 30%.

The mean values (± SD) for the peak TWA levels were 39 ± 19 μV for patients without events (controls), 47 ± 26 μV for all-cause mortality (P = 0.01 in t-test for statistical analysis

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Continuous patient characteristics were compared between those with TWA < 65 and ≥ 65 μV using the t-test for independent samples (Table 1), and the χ² test was applied for dichotomous variables (Table 2).

The relative risks of TWA for all-cause and cardiovascular death as well as for SCD were estimated with a Cox proportional hazards model using the following covariates: sex, age, body-mass index (BMI), daily smoking (yes/no), use of β-blockers (yes/no), functional capacity class according to the New York Heart Association (NYHA), and reached percentage of expected age-adjusted maximal HR (20% to 85%), as well as prior diagnoses of CHD (yes/no), MI (yes/no), diabetes (yes/no), hypercholesterolemia (yes/no), and hypertension (yes/no) (Table 3). The NYHA score, a surrogate for heart failure, was transformed into a dichotomous variable by differentiating the classes with good (II or less) or poor (III) functional class. The statistical analyses were performed with the SPSS release 12.0.1 for Windows (SPSS Inc., Chicago, IL, USA). All statistical tests were two-tailed and used an alpha level of < 0.05. Sensitivity, specificity as well as positive predictive value (PPV) and negative predictive value (NPV) were calculated (Table 4).

Results

During the follow-up period of 44 ± 7 months (mean ± SD), there were 59 deaths (5.7% of the population). Of those, 34 (3.3%) were classified as cardiovascular death and 20 (1.9%) further as SCD. The causes of death for four (0.4%) patients remained unknown. Patient characteristics and number of deaths for those with TWA < 65 μV (n = 950) and TWA ≥ 65 μV (n = 87) are given in Tables 1 and 2. EF for 529 patients was 65 ± 15% (mean ± SD). Only 67 patients (12.7%) had EF < 50%, and only eight patients (1.5%) presented with EF < 30%.

The mean values (± SD) for the peak TWA levels were 39 ± 19 μV for patients without events (controls), 47 ± 26 μV for all-cause mortality (P = 0.01 in t-test for
Mortality and T-wave alternans

The unadjusted prevalence of the three classes of mortality for the patient groups divided by two different TWA cut points (46 and 65 μV) are shown in Figure 1.

Using Cox regression, the unadjusted relative risk for SCD at the cut point of 65 μV was 6.3 (95% CI, 2.5–15.9; \( P < 0.001 \)), for cardiovascular mortality 5.6 (95% CI, 2.7–11.4; \( P < 0.001 \)), and for all-cause mortality 3.3 (95% CI, 1.8–6.1; \( P < 0.001 \)). After adjustments were made for sex, age, BMI, smoking, use of β-blockers, reached percentage of expected maximal HR, dichotomous NYHA class, and for prior diagnoses of CHD, MI, diabetes, hypercholesterolemia, and hypertension, the relative risk for SCD was 7.4 (95% CI, 2.8–19.4; \( P < 0.001 \); Figure 2A), for cardiovascular mortality 6.0 (95% CI, 2.8–12.8; \( P < 0.001 \); Figure 2B), and for death from any cause 3.3 (95% CI, 1.8–6.3; \( P = 0.001 \); Figure 2C). The corresponding values using TWA cut point of 46 μV are presented in Table 3. Sex, BMI, prior MI, and the existence of diabetes were the statistically significant covariates for cardiovascular death, whereas none of the covariates reached significance for SCD (Table 3).

Sensitivity, specificity, as well as PPVs and NPVs are given in Table 4.

**Table 4** Sensitivity, specificity, as well as positive and negative predictive values for sudden cardiac death and for cardiovascular and all-cause mortality using two different T-wave alternans cut points

<table>
<thead>
<tr>
<th>TWA cut point</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 μV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCD</td>
<td>35.0</td>
<td>92.1</td>
<td>8.0</td>
<td>98.6</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>32.4</td>
<td>92.4</td>
<td>12.6</td>
<td>97.6</td>
</tr>
<tr>
<td>All-cause death</td>
<td>22.0</td>
<td>92.4</td>
<td>14.9</td>
<td>95.2</td>
</tr>
<tr>
<td>46 μV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCD</td>
<td>50.0</td>
<td>74.5</td>
<td>3.7</td>
<td>98.7</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>47.1</td>
<td>74.8</td>
<td>6.0</td>
<td>97.6</td>
</tr>
<tr>
<td>All-cause death</td>
<td>33.9</td>
<td>74.5</td>
<td>7.4</td>
<td>94.9</td>
</tr>
</tbody>
</table>

Figure 1 Prevalence of all-cause and cardiovascular mortality as well as sudden cardiac death among patients according to two different cut points (65 and 46 μV) for T-wave alternans. The \( P \)-values are from the \( \chi^2 \) test.

**Discussion**

The findings of the present study, obtained in a large cohort of patients undergoing a clinically indicated exercise test, show that exercise-induced TWA is a strong predictor of cardiovascular mortality, especially of SCD. These observations widen the potential clinical applications of TWA analysis to a more general population of patients not suffering from congestive heart failure and/or depressed left ventricular function.

Previous studies using spectral analysis have consistently shown that positive TWA during the exercise test indicates an increased risk of mortality. The relative risks of mortality for patients with a positive TWA in the present study are comparable with the summary relative risk of 3.8 (95% CI, 2.4–5.9) in 19 studies relating TWA to cardiac arrhythmic events or deaths. In the previous studies, 2398 of the 2608 patients had congestive heart failure, a prior MI, or an implantable cardioverter defibrillator. The studies were therefore performed on populations consisting mostly of high-risk patients, which is also evident in higher cardiovascular mortality, typically 4–10% per year, compared with the 0.9% per year in the current study. The EF data provide another indication that our patients were in a low-risk category compared with the populations studied previously. EF is normal for the great majority of the present cases. It is probable that those in whom EF was not measured had even better cardiovascular health, because there was no need for EF determination. The literature indicates that EF is an arrhythmia risk stratifier only when the EF levels are below normal.

In our study, elevated TWA specifically identified patients at increased 3–4-year risk of SCD. The SCD in a general population with no congestive heart failure is most commonly caused by ventricular fibrillation triggered by an ischaemic event. Therefore, it is plausible to speculate that the presence of TWA during an exercise test reflects the existence of abnormal repolarization making the heart vulnerable to ventricular fibrillation at the time of an ischaemic event. The majority of animal and clinical studies have shown that TWA is caused by underlying regional inhomogeneities of ventricular repolarization predisposing to ventricular...
arrhythmias. Prior clinical studies have mostly included patients with a specific substrate for ventricular tachyarrhythmia, such as infarct scar or heart failure. In the present study, a large proportion of patients presented with TWA without a prior infarction or congestive heart failure, suggesting that elevated TWA can also be present in hearts without an evident structural substrate for life-threatening arrhythmia.

Previous studies have typically employed special electrodes and the spectral analysis technique in the analysis of TWA. We used standard electrodes and a time-domain TWA method, MMA analysis, which is capable of analysing the data with fluctuating HRs. The methodology incorporates an incremental update factor, which is used in constructing the average beat. We tested the incremental update factor values of 1/32 and 1/8, and the latter proved superior in predicting mortality, when a cut off value of HR <125 b.p.m. was used. However, the methodology was relatively robust in adjusted Cox regression analyses with either of the two incremental update factor values: TWA remained as a significant harbinger of cardiovascular and SCD at any of the cut points applied (data not shown for 50, 60, and 70 μV).

MMA analysis of TWA has previously been employed with ambulatory ECGs to stratify arrhythmia risk in a low-risk population of post-MI patients. Nested case–control analysis revealed 4–7-fold higher odds of life-threatening arrhythmias with TWA cut points of 46–53 μV, depending on the lead selected. The results of that preliminary study are remarkably comparable to those of the present, much larger general population-based investigation. These observations underscore the robustness of the MMA method and its utility in both ambulatory ECG monitoring and exercise testing. Recent findings by Shusterman et al. further underscore the potential utility of MMA and other time-domain-based methods in detecting surges in TWA immediately prior to life-threatening ventricular tachyarrhythmias.

The NPV of the present data (Table 4) is highly comparable with the results of the spectral method, for which the NPV averages 97.2 (with a range of 96.5–97.9). PPV is calculated with reference to the prevalence of the particular disease in the population studied. For this reason, the three studies in lower risk post-MI patients reviewed by Gehi et al. reported a PPV of 6.0 (95% CI, 4.5–7.4) for cardiac arrhythmic events. Thus, the PPV in the present study (Table 4) is comparable or even better than that summarized by Gehi et al.

There are some study limitations that may prevent the generalization of the present results. The definition of SCD is never clear-cut. We used death within 24 h after the onset of symptoms as a definition for SCD. It is possible that some of these deaths are not due to ventricular tachyarrhythmia. However, TWA was a strong predictor of cardiovascular mortality but did not predict well the non-cardiac deaths, showing that the occurrence of TWA during exercise reflects abnormal cardiac electrical or mechanical function predisposing to cardiac death. Another limitation is that we do not have information on changes in parameters affecting mortality risk (e.g. smoking, lifestyles, and medication) during the follow-up.

In conclusion, TWA assessed with the time-domain MMA method and standard electrodes during a routine exercise...
test is a promising candidate for a clinically useful prognostic marker. Elevated TWA seems specifically to predict an increased 3-4-year risk of SCD. The prediction of SCD in a general population is a challenge, because a large cumulative number of SCDs occur among patients with no evidence of congestive heart failure or prior MI. A combination of positive TWA and other markers validated in low-risk populations could then be used to screen patients for an increased risk of SCD. More aggressive preventive strategies should then be recommended and applied to those patients.

Acknowledgements

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Conflict of interest: W.K. is an employee of GE Healthcare Information Technologies, Freiburg, Germany. R.L.V. is co-inventor of Cardiovascular Research, the Academy of Finland (grant no. 465-369).

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