T Wave Alternans and Ventricular Arrhythmias in Arterial Hypertension

Marcus G. Hennersdorf, Verena Niebch, Christian Perings, Bodo-E. Strauer

Abstract—Patients with a positive microvolt-level T wave alternans (TWA) are characterized by an increased risk of ventricular tachyarrhythmias. Arterial hypertension leads to an increase of sudden cardiac death risk, particularly if left ventricular hypertrophy is present. The aim of this study was to investigate the value of TWA in patients with arterial hypertension. Fifty-one consecutive patients were included in the study. TWA analysis was performed with patients sitting on a bicycle ergometer and exercising with a gradual increase of workload to maintain a heart rate of at least 105/min. After recording 254 consecutive low-noise-level heartbeats, the exercise test was stopped. The ECG signals were digitally processed by a spectral analysis method. The magnitude of TWA was measured at a frequency of 0.5 cycle per beat. A TWA was defined as positive if the ratio between TWA and noise level was >3.0 and the amplitude of the TWA was >1.8 \( \mu \text{V} \). Eight of the 51 patients (16%) showed a positive TWA. If left ventricular hypertrophy was present, the prevalence of TWA was higher (33.3% versus 8.3%; \( P < 0.05 \)). Sensitivity concerning a previous arrhythmic event was 73%, and specificity was 100%. The alternans ratio was significantly higher in patients with a previous event (39.3±62.3 versus 2.4±4.6; \( P < 0.001 \)), as was the cumulative alternans voltage (4.7±4.1 versus 1.6±1.9 \( \mu \text{V} \); \( P < 0.001 \)). In 16 patients invasively investigated by an electrophysiological study, a significant correlation between inducibility of tachyarrhythmias and a positive TWA result was found (Spearman \( R = 0.36, \ P = 0.01 \)). We conclude that the arrhythmic risk of patients with arterial hypertension is markedly increased if microvolt-level TWA is present. The prevalence of TWA is higher in patients with left ventricular hypertrophy. (Hypertension. 2001;37:199-203.)

Key Words: T wave alternans | arrhythmia | hypertension, arterial

The analysis of T wave alternans (TWA) was introduced recently as a new diagnostic tool for identification of patients with an increased risk of ventricular tachyarrhythmia or sudden cardiac death.1,2 The first data in a representative patient cohort were reported by Rosenbaum et al,2 who found a significant correlation between the occurrence of TWA and the inducibility of tachyarrhythmias in an electrophysiological study. Furthermore, a high percentage of patients with a positive TWA suffered from acute arrhythmic events. The positive predictive value of an acute arrhythmic event was as high as the positive predictive value of the electrophysiological study. However, two thirds of the patients in the reported cohort had coronary heart disease. In contrast, patients with idiopathic hypertrophic cardiomyopathy show a positive TWA if they are in a high-risk group (eg, nonsustained ventricular tachycardia, syncope, familial hypertrophic cardiomyopathy), whereas a negative TWA result indicates a low-risk group.3

Patients with arterial hypertension, particularly those with left ventricular hypertrophy, are characterized by an increased risk of ventricular arrhythmias or sudden cardiac death.4,5 However, the value of TWA in those patients has not been reported. This study describes the results of the impact of TWA in patients with arterial hypertension.

Methods

Patient Population
Fifty-one patients were included in this study. In all patients arterial hypertension had been present for >2 years. All patients were under treatment with angiotensin-converting enzyme inhibitors, calcium antagonists, or diuretics alone or in combination. Patients under treatment with \( \beta \)-blockers were not included because of methodological problems of TWA analysis (see below). Coronary artery disease was excluded by invasive coronary angiography. The patient population was divided into a group of 11 consecutive patients who had survived arrhythmic events or cardiogenic syncope (group A) and a group of 40 consecutive patients without documented ventricular arrhythmias (group B). All patients were investigated as a result of their clinical symptoms (arrhythmia, dyspnea, anginal pain).

None of the patients had an intraventricular obstruction. All patients were noninvasively investigated by conventional 2-dimensional and M-mode echocardiography and conventional bicycle ergometry. Left ventricular hypertrophy was defined as a muscle mass index of \( >125 \text{g/m}^2 \).6–8 Additionally, the muscle mass was indexed to height to avoid influences of obesity.7 Invasive coronary angiography and left ventricular angiography were performed in all patients with angina pectoris or pathological bicycle ergometry. In 20 patients a 24-hour Holter ECG could be analyzed for comparison of spontaneous arrhythmias with the TWA test result.

Exclusion criteria were the presence of atrial fibrillation or flutter or a bundle branch block. Patients who were not able to reach a sufficient workload during ergometry were not included in the study.
Furthermore, the intake of heart rate–slowing substances such as β-blockers led to exclusion from the study if the heart rate did not increase during exercise to at least 105/min.

In 16 patients an electrophysiological study was performed. Up to 3 extrastimuli were delivered from up to 2 right ventricular sites. Electrophysiological tests were considered positive if >6 consecutive monomorphic beats were inducible.

All patients gave written informed consent. There were no objections to the study from an ethical point of view.

TWA Analysis

The analysis was performed during submaximal exercise (CH 2000, Cambridge Heart Inc) with the patients sitting on a bicycle ergometer (SECA). Because of the low amplitude of the TWA, particular attention was paid to ensure adequate signal quality. First the skin was prepared carefully. Fourteen electrodes were placed on the body surface in Einthoven’s, Goldberger’s, and Frank’s mode. Seven of these electrodes were multisegment electrodes (HiRes, Cambridge Heart Inc) for reduction of the noise level. The remaining 7 electrodes were conventional Ag/AgCl electrodes (3 mol/L). After electrode placement, the electrode-to-skin impedance was measured, and the investigation was only started if the impedance was <3 kΩ. ECG signals were amplified and filtered (bandwidth, 0.05 to 250 Hz) and digitized (1000 Hz with 16-bit resolution). The patients exercised with a gradual increase of workload to maintain a heart rate of ≥105/min. Workload was increased in a stepwise fashion to avoid a sudden increase of the heart rate, which could provoke a false-positive test result. If there was neither a high noise level under exercise nor extra beats >10% nor a heart rate <105/min or >145/min, 254 consecutive heartbeats were recorded. The ECG signals were digitally processed by a spectral analysis method. The beat domain power spectrum of the T wave (J point+60 ms through end of the T wave) was calculated every 16 beats from sequential overlapping 128-beat sequences. The magnitude of the TWA was measured at a frequency of 0.5 cycle per beat. The analysis could not be performed if there were other influences with a frequency of 0.5 cycle per beat (ie, respiration rate, pedaling rate, bigeminy). Respiration rate and pedaling rate were recorded during the whole study. Patients were instructed to hold a pedaling rate of 0.33 or 0.66 cycle per beat to avoid interference.

A TWA was prospectively defined to be positive if the ratio between TWA magnitude and noise level was >3 and the cumulative voltage of the TWA was >1.8 μV.6,10 Initially, 55 patients were included in the study, but in 4 of them it was not possible to perform a proper TWA analysis because the noise level was too high or there were too many extra beats or other interference with a frequency of 0.5 Hz. Consequently, these 4 patients were excluded from the study because of these methodological problems.

Statistical Analysis

Nonparametric tests were used to compare data of 2 groups (Mann-Whitney U test, Spearman rank order correlation). A test was considered significant at P < 0.05. The SPSS software package (version 8.0.1) was used for the analysis. Statistical calculations concerning TWA were only made if results of the TWA test were determinate.

Results

In the whole study group, 8 patients (16%) showed a positive TWA (Figures 1 and 2). The mean ratio was 10.38 (range, 0 to 195.42). A positive TWA was detectable in up to 12 leads (mean, 1.2 leads). The prevalence of a positive TWA test result was higher in patients with left ventricular hypertrophy than in patients without (33.3% versus 8.3%; P = 0.05) (Figure 3). The wall thickness was significantly higher in patients with positive TWA (14.4 ± 8.7 versus 10.8 ± 1.2 mm; P < 0.05), and the muscle mass index was markedly different between both groups (188.15 ± 113.86 versus 141.14 ± 37.37 g/m² [P = 0.09] and 190.36 ± 128.46 versus 148.32 ± 37.07 g/m² [P = 0.10]) (Table 1).

Correlation With Previous Arrhythmic Events

In the whole study group, 5 patients were successfully resuscitated from sudden cardiac death before admission to the hospital. Four patients had documented sustained ventricular tachycardias, and in 2 patients syncope was most probably due to an arrhythmic event (group A, Table 2). A significant correlation between patients with a positive TWA and a survived arrhythmic event (P < 0.0001) could be found (Figure 4). None of the patients of group B had a positive alternans tracing (Figure 4). Patients of group A showed a significantly higher ratio (39.3 ± 62.3 versus 2.4 ± 4.6; P < 0.001). The alternans was detectable in significantly more leads (4.31 ± 1.09 versus 0.20 ± 1.09; P < 0.001). Moreover, the alternans voltage was 4.7 ± 4.1 μV in patients with an event in contrast to 1.6 ± 1.9 μV (P < 0.001) in patients without an event (Figure 5).

The sensitivity of a survived arrhythmic event was 73%, and the specificity was 100%. Sensitivity and specificity were only computed if a determinate TWA was present and not in case of indeterminate TWA.

Correlation With 24-Hour Holter ECG

In 20 patients, a 24-hour Holter ECG was performed. Patients with positive TWA showed a higher, but not significantly different, degree of ventricular premature complexes than those with a negative test result (656.6 ± 787.8 versus 306.2 ± 857.7 ventricular premature complexes; P = NS). The number of couplets or nonsustained ventricular tachycardias did not differ between both groups.
Correlation With Inducibility of Ventricular Tachycardia During Electrophysiological Study

Sixteen patients were investigated by invasive electrophysiological testing, of whom 8 patients were in group A and 8 in group B. Three of these patients had inducible monomorphic ventricular tachycardias. Two of the patients with a positive electrophysiological study (inducible ventricular tachycardia/ventricular fibrillation) showed a positive TWA (66%) (Figure 6). In contrast, patients with a negative electrophysiological study had a negative alternans tracing in 77%. The positive predictive value concerning an inducible ventricular tachycardia/ventricular fibrillation was 40%, and the negative predictive value was 91%. The sensitivity of the electrophysiological study concerning a survived arrhythmic event was 38%, and the specificity was 100% (8 patients). The ratio and the cumulative alternans voltage were not significantly different between patients with and without a pathological electrophysiological test result (15.8 ± 11.9 versus 14.1 ± 33.9 μV and 2.0 ± 1.44 versus 2.3 ± 2.9 μV, respectively) because of the high ratio and voltage of the 2 TWA-positive patients in the noninducible group.

Discussion

Analysis of TWA was introduced into clinical practice as a new method to evaluate patients with an increased risk of ventricular arrhythmia. Originally, a macroscopic TWA was associated with a high risk of ventricular tachyarrhythmia. In the 1980s, analysis of the microvolt-level TWA became possible. The first clinical results were published in 1994 by Rosenbaum et al., who found a significant correlation between patients with inducible tachyarrhythmias in the electrophysiological study and positive TWA test result (15.8 ± 11.9 versus 14.1 ± 33.9 μV and 2.0 ± 1.44 versus 2.3 ± 2.9 μV, respectively) because of the high ratio and voltage of the 2 TWA-positive patients in the noninducible group.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TWA Positive (n=12)</th>
<th>TWA Negative (n=48)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>45.6±12.2</td>
<td>48.8±11.7</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>51.1±4.5</td>
<td>52.5±6.1</td>
<td>NS</td>
</tr>
<tr>
<td>Wall thickness, mm</td>
<td>14.4±8.7</td>
<td>10.8±1.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Muscle mass index, g/m²</td>
<td>188.15±113.86</td>
<td>141.14±37.37</td>
<td>0.09</td>
</tr>
<tr>
<td>Muscle mass index, g/m</td>
<td>190.36±128.46</td>
<td>148.32±37.07</td>
<td>0.10</td>
</tr>
<tr>
<td>LVH present, %</td>
<td>62.5</td>
<td>23.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>60.7±7.9</td>
<td>58.4±10.9</td>
<td>NS</td>
</tr>
<tr>
<td>VPB</td>
<td>656.6±787.8</td>
<td>306.2±857.7</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

LVEDD indicates left ventricular end-diastolic diameter; LVH, left ventricular hypertrophy; and VPB, ventricular premature beats during Holter ECG.

<table>
<thead>
<tr>
<th>TABLE 1. Noninvasively Determined Variables in Patients With Arterial Hypertension and Positive or Negative TWA Test Result</th>
</tr>
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<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>LVEDD, mm</td>
</tr>
<tr>
<td>Wall thickness, mm</td>
</tr>
<tr>
<td>Muscle mass index, g/m²</td>
</tr>
<tr>
<td>Muscle mass index, g/m</td>
</tr>
<tr>
<td>LVH present, %</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
</tr>
<tr>
<td>VPB</td>
</tr>
</tbody>
</table>

LVH indicates left ventricular hypertrophy.

TABLE 2. Clinical and Echocardiographic Characteristics of 51 Patients With Arterial Hypertension

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (n=11)</th>
<th>Group B (n=40)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
<td>7/4</td>
<td>27/13</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>45.1±11.2</td>
<td>49.3±12.4</td>
<td></td>
</tr>
<tr>
<td>Survived SCD</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Sustained VT</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>58.0±9.5</td>
<td>59.2±10.7</td>
<td></td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>53.1±5.5</td>
<td>52.0±6.1</td>
<td></td>
</tr>
<tr>
<td>LVESEd, mm</td>
<td>33.0±8.4</td>
<td>30.0±4.5</td>
<td></td>
</tr>
<tr>
<td>Wall thickness, mm</td>
<td>13.1±7.5</td>
<td>10.9±1.2</td>
<td></td>
</tr>
<tr>
<td>Muscle mass index, g/m²</td>
<td>177.69±99.78</td>
<td>140.24±35.24</td>
<td></td>
</tr>
<tr>
<td>Muscle mass index, g/m</td>
<td>179.91±110.40</td>
<td>147.86±35.48</td>
<td></td>
</tr>
</tbody>
</table>

SCD indicates sudden cardiac death; VT, ventricular tachycardia; LVEDD, left ventricular end-diastolic diameter; and LVESEd, left ventricular end-systolic diameter. There were no significant differences between groups.

Figure 2. Representative TWA voltage of a patient with previous ventricular tachycardia. The dark shaded areas for each lead indicate regions for which the voltage has a ratio >3. In this patient the alternans became positive in leads eV4, eV5, and eV6. The alternans voltage was 2.9 to 4.7 (first number), and the ratio was 3.7 to 15.1 (second number). Alternans voltage increased with increasing heart rate (HR). % bad indicates percentage of bad beats (ventricular premature beats).

Figure 3. Percentage of TWA in patients with arterial hypertension with or without additional left ventricular hypertrophy (LVH).
trophysiological study and a positive TWA. Furthermore, they performed a prospective follow-up investigation and calculated a positive predictive value of a positive TWA of 70% in contrast to 65% with the electrophysiological study. The Kaplan-Meier survival curves were similar regarding a positive TWA or a pathological electrophysiological test result. However, the reported patient cohort consisted predominantly of patients with coronary artery disease (66%). Furthermore, 73% of the investigated patients had a documented history of ventricular tachyarrhythmias or syncope. Consequently, this patient cohort was already at increased risk. In patients with an implanted cardioverter defibrillator, TWA is a powerful predictor of appropriate therapy with this device. In the study of 95 patients by Hohnloser et al., TWA was the only independent risk factor of an ECG-documented ventricular tachycardia or fibrillation.

Very few data are available on TWA measurement in patients with nonischemic cardiomyopathies. Momiyama et al. found a significant correlation between a positive TWA and the existence of clinical characteristics indicating a higher arrhythmic risk (documented nonsustained ventricular tachycardia, syncope, and familial occurrence of sudden cardiac death) in patients with idiopathic hypertrophic cardiomyopathy. A predictive risk stratification was not possible with sufficient accuracy, however (positive predictive value 81%, negative predictive value 53%). Recently, Adachi et al. reported on 58 patients with dilated cardiomyopathy and found a positive correlation between the presence of nonsustained and sustained ventricular tachycardia during Holter ECG and a pathological TWA test result. They did not investigate patients with prior cardiac arrest.

This study describes the impact of a positive TWA in patients with arterial hypertension. Such a patient cohort is difficult to investigate by noninvasive testing.15,16 The invasive electrophysiological study can help to reproduce sustained ventricular tachyarrhythmias in a certain percentage of patients with prior documented ventricular tachycardia/ventricular fibrillation, but the prognostic accuracy in hypertensive patients is weak.17 In this entity of heart muscle disease the analysis of TWA may be a new parameter for risk stratification. We found a significant correlation between a positive TWA and a history of survived arrhythmic events. The sensitivity was 73%, and the specificity was 100%. In contrast, the invasive electrophysiological study showed a sensitivity of 38% for an arrhythmic event. A positive result of the electrophysiological test was predicted by a positive TWA in 40%. Furthermore, patients with a positive TWA showed more ventricular premature complexes. If left ventricular hypertrophy is present, the prevalence of TWA is increased (33.3% versus 8.3% in patients without hypertrophy). In a follow-up period of 6 months only 1 patient had an arrhythmic event, but this patient presented with a positive TWA test result.

The underlying mechanism of a positive TWA probably is an alteration in action potential morphology or dispersion of repolarization. It has been postulated that the changes in morphology of the action potentials may lead to spatial inhomogeneity in refractoriness and increased vulnerability to ventricular fibrillation. During repeated ischemia, an action potential alternans was detectable in 95% of the cases with ventricular fibrillation.18 The dispersion of repolarization is closely related to a temporospatial pattern of depolarization-repolarization, which can alternate on a beat-to-beat basis. Following this hypothesis, the temporospatial dispersion of cellular refractoriness predisposes the myocardium to wavefront fractionation and subsequent reentry.19 The TWA can be influenced by hypothermia, ischemia, heart rate, and sympathetic tone.18,20,21 Alternans magnitude can be reduced by procainamide22 and amiodarone,23 and sotalol can lead to the conversion of TWA from negative to positive.24 In the case of cardiomyopathies, the development of small areas of scars and ischemia17,25 is considered to be of pathological relevance for the development of alterations in action potentials or dispersion of repolarization.

The method used to examine TWA can be practiced to ensure a good result. If preparation of the patient’s skin is performed carefully and if the patients are properly selected (no β-blockers, sufficient capacity for ergometry), the test can be performed in 91%. However, patients with cardiomyopathies and reduced left ventricular function often are treated with β-blockers and are not able to complete ergom-
etry; the applicability of the TWA test is therefore limited in those patients.

Limitations
There is a strong correlation between prior arrhythmic events and positive test results. However, because of the small number of arrhythmic events during the follow-up period (1 patient), the prognostic significance of TWA cannot be calculated in this study. Prospective studies in large patient cohorts are necessary to evaluate the prognostic relevance of the analysis of TWA. Furthermore, the influence of regression of hypertrophy on the prevalence of TWA must be evaluated in those patients.

In conclusion, the analysis of a microvolt-level TWA may be helpful for risk stratification of patients with arterial hypertension. The sensitivity for identification of patients at risk in this study was 73%. It is likely that a combination of several noninvasive investigation methods concerning autonomic tone (baroreflex sensitivity/chemoreflex sensitivity), depolarization disturbances (ventricular late potentials), and repolarization disorders (TWA) can lead to the identification of patients at risk with sufficient accuracy to allow treatment with specific antiarrhythmic therapy.

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