Microvolt T-Wave Alternans as a Predictor of Ventricular Tachyarrhythmias
A Prospective Study Using Atrial Pacing

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Background—Microvolt T-wave alternans (TWA) is reported to be closely associated with sudden cardiac death (SCD) and ventricular tachycardia (VT). Animal experiments revealed that microvolt TWA is highly dependent on heart rate. The purpose of this study was to determine whether patients with TWA at relatively low heart rates have increased vulnerability to ventricular tachyarrhythmias.

Methods and Results—Subjects were 248 consecutive patients (158 men, 90 women; mean age, 59±17 years) who underwent electrophysiological study from 1997 to 2000. TWA recording was made in sinus rhythm and at atrial pacing rates of 90, 100, 110, and 120 bpm with the Cambridge Heart CH2000 system. Alternans voltage (V_{alt}) was measured when the alternans ratio was >3 for a period of >1 minute in VM, X, Y, Z, or 2 adjacent precordial leads. Study end point was the first appearance of VT, ventricular fibrillation (VF), appropriate implantable cardioverter-defibrillator therapy with pacing or shocks, or SCD. During the 37±12-month follow-up period, 22 patients had sustained VT, and 5 patients died of SCD. In patients with >1.9-μV V_{alt} at rates of 90, 100, and 110 bpm, the incidence of VT/VF/SCD was 56%, 28%, and 18%, respectively. V_{alt} of >2.9 μV at a heart rate of 90 bpm had a 70% positive predictive value for VT/VF/SCD. However, when V_{alt} was <0.9 μV at a rate of 120 bpm, negative predictive value was 100%.

Conclusions—Patients with TWA at relatively low heart rates are susceptible to ventricular tachyarrhythmias.

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Key Words: death, sudden heart rate T-wave alternans tachycardia, ventricular fibrillation, ventricular

Microvolt T-wave alternans (TWA) has been reported to be closely associated with sudden cardiac death (SCD) and ventricular tachycardia (VT). We have shown that TWA is highly dependent on heart rate and that patients with organic heart disease and ventricular tachyarrhythmia have TWA onset at lower heart rates than do patients without organic heart disease. Animal experiments have shown that the magnitude of microvolt TWA is correlated with ventricular fibrillation (VF) threshold. TWA is a heart rate–dependent marker of vulnerability to VT. However, there is only 1 study in which heart rate was used as a marker of risk stratification to classify high-risk patients. The heart rate at which alternans voltage (V_{alt}) exceeds positivity criteria is called the onset heart rate. Kitamura et al showed that the onset heart rate of microvolt-level TWA provides clinical and prognostic value in nonischemic dilated cardiomyopathy. The purpose of this study was to test the hypothesis that patients with TWA onset at relatively low onset heart rates have increased vulnerability to VT.

Methods

Patient Characteristics

This was a prospective, single-center study that enrolled 248 consecutive patients who underwent electrophysiological study (EPS) at Showa University Hospital from 1997 to 2000. The inclusion criteria were age ≥21 years and referral for EPS. The exclusion criteria were current use of Vaughan-Williams class I, II, or III antiarrhythmic drugs, myocardial infarction <1 month old, and inability to pace the atrium continuously. All patients gave informed consent.

Measurement of TWA

TWA testing was conducted for patients in the postabsorbed state in a sealed room on the day after EPS. A 5F hexapolar catheter was introduced through the left subclavian vein and positioned at the high right atrium for continuous pacing of the heart. Careful skin preparation was performed to reduce skin-electrode impedance. Special high-resolution electrodes (High-Res, Cambridge Heart, Inc) were used to minimize noise. ECG leads were placed at the standard precordial lead positions and in an orthogonal X, Y, Z configuration. TWA recordings were made with the CH2000 system (Cambridge Heart, Inc) with the patient in sinus rhythm and under high right atrial pacing at 90, 100, 110, and 120 bpm if conduction proceeded without AV block for >3 minutes at each pacing rate. A spectral
Follow-Up
Patients were followed up prospectively at our university hospital outpatient clinic every month. The primary end point of the study was the combined incidence of sustained VT, VF, appropriate implantable cardioverter-defibrillator (ICD) therapy with pacing or shocks, or SCD. Fifty patients received ICDs in this study, and stored ICD electrograms were used in the evaluation of therapy.

Statistical Analysis
Kaplan-Meier survival curves were used to estimate the cumulative percentage of patients surviving free from end-point events over time. Comparisons between survival curves were made by use of the log-rank statistic. A value of P<0.05 was considered statistically significant.

Results

Patient Population
There were 158 men and 90 women. Mean age was 59±17 years. One hundred twenty-three patients had organic heart disease: ischemic heart disease, n=7; hypertensive heart disease, n=25; hypertrophic cardiomyopathy, n=18; dilated cardiomyopathy, n=12; valvular heart disease, n=7, arrhythmogenic right ventricular cardiomyopathy, n=4; postmyocarditis, n=3; other (cardiac amyloidosis, congenital pulmonary stenosis, tetralogy of Fallot), n=3. One hundred twenty-five patients had no structural heart disease. Twelve patients had cardiomyogenic right ventricular cardiomyopathy, n=7, arrhythmogenic right ventricular cardiomyopathy, n=4; postmyocarditis, n=3; other (cardiac amyloidosis, congenital pulmonary stenosis, tetralogy of Fallot), n=3. One hundred twenty-five patients had no structural heart disease. Twelve patients had

Valt and Heart Rate
The results of TWA testing are shown in Figure 1. At each voltage criterion, the percentage of positive TWA increased as the pacing heart rate increased. However, at each voltage criterion, the percentage of negative TWA decreased as the pacing heart rate increased. In addition, as the voltage criterion increased, the percentage of positive TWA increased as the pacing heart rate increased. However, at each voltage criterion, the percentage of negative TWA decreased as the pacing heart rate increased. Valt increased at every heart rate.

Follow-Up
During a mean follow-up period of 45±12 months, sustained VT or VF occurred in 22 patients, and 5 patients were diagnosed as having SCD. VT or VF was confirmed in stored ECGs of the ICD in 14 of 22 patients. Characteristics of the study population are shown in Table 1.

VT/VF/SCD and Valt
The incidence of VT, VF, or SCD in patients with positive TWA testing is shown in Figure 2. At a heart rate of 90 bpm, 25 patients had 1.9-Valt. Of these 25 patients, 10 (40%) had VT/VF/SCD during the follow-up period. Similarly, 18 patients had >1.9-Valt at a rate of 90 bpm. Of these 18 patients, 10 (56%) had VT/VF/SCD. At >2.9-Valt, 7 of 10 patients (70%) had VT/VF/SCD. As the Valt increased, the percentage of patients who suffered from VT/VF/SCD also increased. At pacing rates of 100, 110, and 120 bpm, the percentage of patients with VT/VF/SCD decreased as the pacing heart rate increased.

Event-Free Survival
Event-free survival calculated by the Kaplan-Meier method during the 45 months of follow-up is shown in Figure 3. Patients with TWA whose Valt was >1.9 at a rate of 90 bpm suffered from VT/VF/SCD more frequently than did patients with TWA whose Valt was <1.9. Similarly, VT/VF/SCD occurred more frequently in patients with >1.9-Valt than in patients with <1.9-Valt even at heart rates of 100, 110, and 120 bpm.

Sensitivity and Specificity
The ability of TWA to predict VT/VF/SCD statistically at each heart rate is shown in Table 2. The highest positive predictive value is 70%, when the heart rate is 90 bpm and Valt.

<table>
<thead>
<tr>
<th>TABLE 1. Clinical Characteristics of the Study Population</th>
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<tbody>
<tr>
<td>End Point</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Male, n</td>
</tr>
<tr>
<td>SHD, n</td>
</tr>
<tr>
<td>IHD</td>
</tr>
<tr>
<td>Non-IHD</td>
</tr>
<tr>
<td>Non-SHD, n</td>
</tr>
<tr>
<td>LVEF, %</td>
</tr>
<tr>
<td>Sustained VT, n</td>
</tr>
<tr>
<td>Nonsustained VT, n</td>
</tr>
<tr>
<td>Unexplained syncope, n</td>
</tr>
</tbody>
</table>

SHD indicates structural heart disease; IHD, ischemic heart disease; and LVEF, left ventricular ejection fraction.
is >2.9 μV. The highest negative predictive value is 100%, at a heart rate of 120 bpm and $V_{alt} < 0.9 \mu V$.

**Representative Case**

A representative case of TWA measurement with atrial pacing is shown in Figure 4. The patient is a 46-year-old man with dilated cardiomyopathy who had polymorphic VT induced by programmed electrical stimulation. $V_{alt}$ was >1.9 μV at a rate of 90 bpm and increased with the pacing heart rate. Twenty-two months after TWA testing, he suffered from VF that was terminated by his ICD.

**Discussion**

**TWA and VT**

TWA is a marker of cardiac electrical instability. Adam et al. discovered that the magnitude of microvolt TWA is correlated with VF threshold in experimental animals. Nearing et al. later confirmed that TWA recorded from experimental animals was closely associated with VF. Later, microvolt TWA induced by elevation of heart rate by atrial pacing or moderate exercise was reported to be correlated closely with arrhythmia risk in humans, regardless of the underlying heart disease. However, only a few studies have addressed the influence of heart rate on microvolt TWA. The present study showed that patients who had high $V_{alt}$ at a relatively low heart rate suffered most frequently from VT or SCD. This finding supports the hypothesis that microvolt TWA is correlated with VT in humans.

**Positivity Criteria and VT**

Currently, there is only 1 machine that can measure $V_{alt}$ in the clinical setting. Most clinical studies on microvolt TWA use the same positivity criteria: >1.9 μV of $V_{alt}$ at a heart rate <110 bpm without artifact or noise. Sensitivity was found to be 78% to 93% and specificity was 45% to 61% for predicting VT/VF/SCD according to these criteria. The characteristics of TWA testing by exercise were found to be those of high sensitivity and moderate specificity to predict VT. The heart rate at which $V_{alt}$ exceeds positivity criteria is called onset heart rate. Previously, we retrospectively showed that patients with sustained VT and structural heart disease had lower onset heart rates of microvolt TWA using these criteria. The present prospective study showed that patients with a high $V_{alt}$ at a relatively low heart rate have an increased incidence of VT during follow-up periods. This finding may make it possible to stratify patients by risk. Measurement of $V_{alt}$ at different heart rates may help to differentiate patients who need an ICD from those who do not. The Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) revealed that prophylactic ICD implantation for patients with a prior myocardial infarction and left ventricular dysfunction improved prognoses. In fact, it is not realistic to implant an ICD in all patients who meet the MADIT II criteria. We have

<table>
<thead>
<tr>
<th>Heart Rate, bpm</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>0.9 $\mu V$</td>
<td>71</td>
<td>93</td>
<td>40</td>
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<tr>
<td>1.9 $\mu V$</td>
<td>54</td>
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<td>97</td>
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<td>62</td>
<td>93</td>
<td>38</td>
<td>97</td>
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<td>0.9 $\mu V$</td>
<td>79</td>
<td>71</td>
<td>21</td>
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<tr>
<td>1.9 $\mu V$</td>
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<td>87</td>
<td>28</td>
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<td>62</td>
<td>93</td>
<td>38</td>
<td>97</td>
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<tr>
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<td>21</td>
<td>98</td>
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<tr>
<td>120</td>
<td>0.9 $\mu V$</td>
<td>100</td>
<td>44</td>
<td>9</td>
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<td>2.9 $\mu V$</td>
<td>70</td>
<td>79</td>
<td>19</td>
<td>98</td>
</tr>
</tbody>
</table>

PPV indicates positive predictive value; NPV, negative predictive value. Values are percents.
Onset Heart Rate and VT

There is only 1 study in which onset heart rate was used as a risk factor for VT. That report showed that onset heart rate of patients with VT was lower than that of patients without VT. However, the problem is how to decide the onset heart rate when exercise is used to increase heart rate. Because the CH2000 system uses fast Fourier transformation as the means of alternans measurement, it is necessary to obtain 256 consecutive steady-state beats to measure Valt accurately. When exercise is used to increase heart rate for TWA testing, the heart rate at the beginning of the 256-beat cycle is definitely different from that at the end of the cycle. It is not easy to determine the onset heart rate precisely by exercise. In addition, autonomic nervous tone during atrial pacing at rest differs from that of exercise. It is possible that TWA induced by atrial pacing is different from that induced by exercise because autonomic nervous tones influence TWA. Thus, we chose to use the atrial pacing method to obtain a fixed heart rate, which made it possible to evaluate the effect of heart rate on TWA precisely.

TWA as a Predictor of VT

Although predictive factors for VT/VF/SCD exist, they are not necessarily satisfactory. TWA testing may be a promising predictor for VT. TWA testing for predicting VT is of high sensitivity, moderate specificity, low positive predictive value, and high negative predictive value. With such characteristics, TWA testing would be suitable for screening of patients with structural heart disease. However, Tapanainen et al reported that sustained TWA during the predischarge exercise test after acute myocardial infarction does not indicate increased risk for mortality and that an incomplete TWA test and several common risk factors provided prognostic information in this post–acute myocardial infarction population. Recently, Hohnloser et al reported that MADIT II–type patients who test negative for microvolt TWA may not benefit from defibrillator therapy. Nonetheless, it is probably possible to stratify patients with arrhythmic risk in more detail when Valt is measured precisely at a stable heart rate as we describe here. In the present study, 7 of 10 patients with 2.9 µV of Valt at a heart rate of 90 bpm suffered from VT, whereas 0 of 64 patients with <0.9 µV of Valt at a heart rate of 120 bpm had VT during the follow-up period.

Study Limitations

Several limitations of the present study need to be addressed. First, the sample size is small. Higher numbers may provide additional insight. The second is the variety of heart disease in the patients in this study. Moreover, this study included patients with supraventricular tachyarrhythmia who were at low risk of an event. Finally, appropriate ICD therapies as the end point were used in this study. The use of this end point as a surrogate marker may overestimate the occurrence of events.

TWA is a promising new predictor for VT, but several problems must be resolved. First, the number of patients diagnosed as “indeterminate” was not small. Seven percent of the patients in this study were diagnosed as indeterminate even with the use of atrial pacing at a rate of 90 bpm. The reasons were that heart rate did not increase enough to analyze TWA, heart rate increased too rapidly to analyze TWA, there were frequent ectopic beats, or there was excessive noise. In addition, TWA testing is never applicable in patients with atrial fibrillation.

Conclusions

Patients with relatively low onset heart rate of microvolt TWA have increased vulnerability to VT.

References

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