Predictive Value of Microvolt T-Wave Alternans for Sudden Cardiac Death in Patients With Preserved Cardiac Function After Acute Myocardial Infarction

Results of a Collaborative Cohort Study

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OBJECTIVES
We conducted a collaborative cohort study to evaluate the predictive power of microvolt T-wave alternans (TWA) in patients with preserved left ventricular ejection fraction (LVEF) after myocardial infarction (MI).

BACKGROUND
There is little information available about the prognostic value of risk stratification markers in this population. Although these patients have a relatively good prognosis, identifying high-risk patients is important in clinical practice.

METHODS
This study enrolled 1,041 post-MI patients with an LVEF ≥40% (average 55 ± 10%). Microvolt TWA testing was performed 48 ± 66 days after acute MI, and 10 other risk variables were also evaluated. The end points were prospectively defined as sudden cardiac death or life-threatening arrhythmic events.

RESULTS
During a follow-up of 32 ± 14 months, 38 patients (3.7%) died of nonarrhythmic causes and were not considered for analysis. Of the 1,003 evaluable patients, 18 (1.8%) reached an end point. Microvolt TWA was positive in 169 patients (17%), negative in 747 (74%), and indeterminate in 87 (9%). A positive microvolt TWA test, nonsustained ventricular tachycardia, and ventricular late potentials were predictors of events, and percutaneous coronary intervention decreased the risk rate. On multivariate analysis, a positive microvolt TWA test was the most significant predictor, with a hazard ratio of 19.7 (p < 0.0001). This marker had the highest sensitivity and negative predictive value for events.

CONCLUSIONS
In patients with preserved cardiac function, the incidence of indeterminate results of microvolt TWA is low, and a positive test result is associated with arrhythmic events. Microvolt TWA could be used for risk stratification in this low-risk population. (J Am Coll Cardiol 2006;48:2268–74) © 2006 by the American College of Cardiology Foundation

There are numerous reports regarding risk stratification in patients with reduced left ventricular (LV) function after myocardial infarction (MI) (1–5). In contrast, there is little information available with respect to the prognostic value of risk stratification markers in post-MI patients with preserved LV function. Although the prognosis of patients with preserved cardiac function is better than that of patients with reduced cardiac function, risk stratification in such patients is important in clinical practice.

Previously, we reported that microvolt T-wave alternans (TWA) (6) is associated with an increased risk of arrhythmic events in post-MI patients (7,8). Recently, it has been reported that an “abnormal” microvolt TWA test (i.e., both positive and indeterminate results) is a useful marker for the identification of high-risk patients, and a negative microvolt TWA test is a marker of low risk among post-MI patients with a reduced LV ejection fraction (LVEF) ≤30% (9,10) or <40% (11). However, the prognostic power of microvolt TWA is unknown in post-MI patients with preserved LVEF.

We conducted a large collaborative cohort study involving patients with preserved LVEF after acute MI to evaluate the predictive value of 11 risk variables, including microvolt TWA, for sudden cardiac death and assessed the utility of a positive microvolt TWA test in the identification of high-risk patients in need of an implantable cardioverter-defibrillator (ICD).
METHODS

Patient population. This prospective study enrolled 1,041 consecutive infarct survivors (824 men, mean age 64 ± 11 years) with an LVEF ≥40% at 8 Japanese medical centers (Kyorin University Hospital, Toho University Hospital, Showa University Hospital, Hyogo College of Medicine Hospital, Tohoku University Hospital, Kobe University Hospital, Nihon University Hospital, and Niibara Medical School Hospital) between January 1999 and December 2004. The diagnosis of acute MI was based on clinical course, serum creatine kinase activity, and ST-segment elevation on electrocardiogram. The LVEF was calculated by echocardiography or radionuclide ventriculography if the echocardiogram was difficult to interpret. No patient had heart failure at entry. Patients with persistent atrial fibrillation/flutter or who required a ventricular pacemaker were excluded from the study because the microvolt TWA test cannot be administered in such patients.

Informed consent was obtained from each patient. The study was approved by the institutional review boards of the participating institutions. This study was conducted by the Committee on Body Surface Electrical Potentials Research of the Japanese Society of Electrocardiology.

Measurement of microvolt TWA testing. Microvolt TWA testing was performed using a CH2000 System (Cambridge Heart, Inc., Bedford, Massachusetts) or a HeartWave System (Cambridge Heart, Inc.) during bicycle or treadmill exercise, which allows the detection of microvolt electrical alternans of the T-wave using spectral analysis. The test was performed at least 14 days after the onset of acute MI while patients were taking their antiarrhythmic drugs. The test was performed at least 14 days after the onset of acute MI while patients were taking their antiarrhythmic drugs and/or beta-blockers (mean time since MI onset 48 ± 66 days). The microvolt TWA test was interpreted as positive, negative, or indeterminate according to a previously described report (12). Briefly, the test was defined as positive when the sustained alternans voltage was >1.9 μV with an alternans ratio >3.0 in any orthogonal lead or 2 consecutive precordial leads during exercise with an onset heart rate <110 beats/min for at least 1 min. The test was defined as negative when the positive criteria were not met and artifact-free data were available showing a heart rate maintained at a level >105 beats/min for at least 1 min. The test was defined as indeterminate when the results did not meet either the positive or negative criteria.

Measurements of other variables. In addition to the microvolt TWA test, other prognostic variables for sudden cardiac death were nonsustained ventricular tachycardia (NSVT), ventricular late potentials (LP), an LVEF <45% but ≥40%, age >70 years, gender (male), anterior wall infarction, successful percutaneous coronary intervention, coronary artery bypass graft surgery, antiarrhythmic drug therapy, and beta-blocker therapy. Nonsustained ventricular tachycardia was detected on Holter monitoring during normal daily activities and was defined as the documentation of ≥3 consecutive ventricular premature beats at a rate of 100 beats/min. The ventricular LPs were analyzed using a signal-averaged electrocardiography system (1200EPX [Arrhythmia Research Technology Co., Austin, Texas] or VCM3000/FDX6521 [Fukuda Denshi Co., Tokyo, Japan]) based on quantitative time domain measurements. Three parameters such as f-QRS, RMS40, and LAS40 were assessed via a computer algorithm. The criteria for abnormality of LP in each system were defined previously (7,13,14). When bundle branch block was seen, it was considered indeterminate.

Follow-up and study end points. Clinical follow-up was conducted at 2- or 4-week intervals at each participating institution. During the follow-up period, patients who underwent revascularization procedures in the acute phase of MI had further coronary angiography (i.e., usually 3 or 6 months after MI). When patients had significant restenosis of coronary arteries, coronary interventions were repeated. The end points were prospectively defined as sudden cardiac death, cardiac arrest, or resuscitated ventricular fibrillation; hemodynamically stable sustained ventricular tachyarrhythmias were excluded from the end points. Sudden cardiac death was defined as instantaneous, unexpected death or death within 1 h of symptom onset not related to circulatory failure. Cardiac deaths attributable to non-arrhythmic causes such as subsequent MI were not included as end points and were excluded from the present analysis.

Statistical analysis. Data are expressed as mean ± SD. For the analysis of the association between follow-up events and the 11 clinical variables, univariate and multivariate Cox regression analyses were performed. Results of event-free analyses are presented with hazard ratios and 95% confidence intervals (CI). Sensitivity, specificity, positive and negative predictive values, and the predictive accuracy of event-free prediction were also evaluated. Differences in event-free rates were determined using the Kaplan–Meier method and the log-rank test. A value of p < 0.05 was considered statistically significant.

RESULTS

Patient characteristics. The clinical characteristics of the 1,041 patients are shown in Table 1. Of the 1,041 patients,
653 patients (63%) had an LVEF ≥50% and 288 patients (37%) had an LVEF <50% but ≥40%. A total of 634 patients (61%) had anterior wall infarctions, 333 (32%) had inferior wall infarctions, and 74 (7%) had lateral wall infarctions. A total of 974 patients (94%) underwent primary percutaneous coronary intervention and 53 (5%) underwent coronary artery bypass grafting in the acute phase of MI. Ninety-one patients (9%) received antiarrhythmic drugs (amiodarone in 20 patients [2%], class I antiarrhythmic drugs in the remaining 71 patients [7%]), and 218 patients (21%) were given beta-blockers during the follow-up period. Although the incidence of patients who received class I antiarrhythmic drugs was high, 49 patients (69%) took class IB drugs such as mexiletine and aprindine because of symptoms due to premature ventricular beats. Regarding use of class IA/IC drugs as well as amiodarone, these drugs were used mainly to inhibit paroxysmal atrial tachyarrhythmias.

**Follow-up events.** During follow-up, 83 patients (8%) had significant restenosis of coronary arteries. Coronary interventions were repeated for these patients. Thus, in this population, patients had good revascularization. Although we collected data on a prospective cohort of 1,041 infarct survivors, 38 patients died of nonarrhythmic causes (including cancer [n = 17], pneumonia or other infections [n = 8], stroke [n = 4], subsequent MI [n = 3], and aortic dissection [n = 2]) during the follow-up period. These patients were not considered for the present analysis. Of 1,003 evaluable patients, 18 (1.8%) reached one of the end points during a mean follow-up period of 32 ± 14 months; 14 died suddenly, 2 experienced cardiac arrest, and 2 had resuscitated ventricular fibrillation. Of the 18 patients with arrhythmic events, 2 (11%) received class I antiarrhythmic drugs, and 65 (7%) of 985 patients without events received the drugs. No significant difference was seen between patients with and without arrhythmic events in the incidence of class I drugs (p = 0.34).

**Outcome of microvolt TWA testing.** Microvolt TWA measurements were performed in all 1,003 patients. The microvolt TWA test was positive in 169 patients (18%), negative in 747 (74%), and indeterminate in 87 (9%). We could find a relationship between the mode of revascularization and the outcome of microvolt TWA testing in this clinical setting. The incidence (16%) of a positive test result in patients with percutaneous coronary intervention was lower than that (28%) in patients with coronary artery bypass grafting (p = 0.02). In this study, although 7% of the patients took class I antiarrhythmic drugs, there was no relationship between use of class I drugs and the outcome of microvolt TWA testing.

Indeterminate results were primarily due to frequent ectopic beats or the inability to achieve the target heart rate of >105 beats/min. In this patient population with prior MI and a preserved LVEF ≥40%, the incidence of an indeterminate test result on microvolt TWA was lower than that in patients with prior MI and a reduced LVEF (9–11). Therefore, we separated patients with a positive microvolt TWA test from patients with an indeterminate microvolt TWA test; most previous reports in the MI population with reduced LV function have combined these two groups into one “abnormal” group. In this low-risk population, patients with an indeterminate test result had no serious arrhythmic events.

**Outcome of other variables.** Twenty-four-hour Holter monitoring was analyzed in 954 of 1,003 patients. At least one episode of NSVT was found in 112 patients (12%). Signal-averaged electrocardiography was performed in 907 patients; the LP was positive in 81 patients (9%), negative in 807 (89%), and indeterminate in 19 (2%). Indeterminate results in LP were due primarily to a prolonged QRS interval (>120 ms). An LVEF <45% but ≥40% was found in 175 of the patients.

**Prediction of event-free survival.** Of the 11 risk variables, univariate Cox regression analysis revealed that a positive microvolt TWA test, NSVT, ventricular LP, and lack of percutaneous coronary intervention were associated with serious arrhythmic events (Table 2). A reduced LVEF (i.e., <45% but ≥40%) was not in this population. A positive microvolt TWA test predicted serious arrhythmic events with a hazard ratio of 23.5 (95% CI 6.8 to 81.0; p < 0.0001). Hazard ratios for NSVT and ventricular LP were 6.2 (p = 0.0001) and 5.8 (p = 0.0006), respectively. Patients who underwent percutaneous coronary intervention at acute phase of MI had a significantly lower risk, with a hazard ratio of 0.3 (p = 0.04). To test the statistical significance of a positive microvolt TWA test in predicting arrhythmic events, multivariate Cox regression analysis was performed (Table 2). A positive microvolt TWA test had the most significant value, with a hazard ratio of 19.7 (95% CI 5.5 to 70.4; p < 0.0001). Event-free survival rates of microvolt TWA, NSVT, and ventricular LP calculated by the Kaplan-Meier method during follow-up are shown in Figure 1. Patients with a negative microvolt TWA test had
few events, whereas patients with NSVT or ventricular LP had several events. In predicting serious arrhythmic events, the sensitivity of a positive microvolt TWA test was markedly higher than that of NSVT or ventricular LP, although the other predictive values did not differ markedly among these 3 markers (Table 3).

Because class I antiarrhythmic drugs are relatively contraindicated owing to their potential proarrhythmic hazards (15), we reanalyzed data in a patient population (n = 936) without patients who received class I drugs. Even in this population, a positive microvolt TWA test was associated with serious arrhythmic events, with a hazard ratio of 20.5 (95% CI 5.8 to 71.8; p < 0.0001). We also performed multivariate Cox regression analysis to test the statistical significance of a positive microvolt TWA test. The test had the most significant value, with a hazard ratio of 15.8 (95% CI 4.2 to 59.1; p < 0.0001). In patients without class I drugs, a positive microvolt TWA test had sensitivity of 81%, specificity of 83%, positive predictive value of 8%, negative predictive value of 99.6%, and predictive accuracy of 83% in predicting arrhythmic events (Table 3).

DISCUSSION

This prospective study is the first to show the prognostic value of microvolt TWA compared with various other known risk variables in patients with preserved LV function after acute MI. The results reveal that a positive microvolt TWA test is the most significant predictor of sudden cardiac death or life-threatening arrhythmic events.

Risk stratification in patients with preserved cardiac function. Serious ventricular tachyarrhythmias are the most common mechanism of sudden cardiac death after acute MI (16). In the era of revascularization at the acute phase of MI, the risk of sudden cardiac death among post-MI patients is considered to be low, particularly in patients with preserved cardiac function. In this study, the incidence was 1.8% during a mean follow-up period of 32 months. As shown in previous studies (17), revascularization therapy could influence the prognosis of infarct survivors. In fact, this study showed that primary percutaneous coronary intervention was associated with a clinically significant decrease in the incidence of serious arrhythmic events. In this study, when patients had significant restenosis of coronary arteries during follow-up, coronary interventions were repeated. This revascularization strategy may also influence a lower incidence of arrhythmic events. The observed results may apply to a population of coronary patients with good revascularization.

In general, patients with preserved cardiac function have a lower incidence of arrhythmic events than patients with reduced cardiac function. However, clinical management of patients with preserved cardiac function is important because arrhythmic events can occur unexpectedly in this patient population. It is currently possible to prevent sudden cardiac death by ICD therapy. Primary prevention of sudden cardiac death with ICD therapy requires risk stratification and identification of high-risk subgroups. At present, there are no strategies to identify patients at risk for sudden cardiac death in populations with preserved cardiac function after MI. In this study, a positive microvolt TWA test, NSVT on Holter monitoring, and ventricular LP analyzed by signal-averaged electrocardiography were all significant predictors of sudden cardiac death or life-threatening arrhythmic events, with a positive microvolt TWA test the most significant predictor. These results appear to be useful for the selection of patients in need of ICD therapy. Interestingly, a reduced LVEF <45% but ≥40% was not associated with serious arrhythmic events. In populations with preserved cardiac function after MI, an LVEF may not be useful in identifying patients at risk.

Interpretation of microvolt TWA in low-risk populations. Some very large trials, such as the MADIT (Multicenter Automatic Defibrillator Implantation Trial) II and a subanalysis of the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial), have established that prophylactic ICD therapy improves the survival rate over that with conventional medical therapy in patients with reduced LVEF after MI (18,19). It has been reported that microvolt TWA is associated with an increased risk of ventricular arrhythmia in several clinical settings (6–10,20–24). Following an

Table 2. Statistical Association of 11 Risk Variables With Serious Arrhythmic Events in Univariate and Multivariate Analyses

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>p Value</td>
</tr>
<tr>
<td>Microvolt T-wave alternans</td>
<td>23.5 (6.8–81.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nonsustained ventricular tachycardia</td>
<td>6.2 (2.5–15.8)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ventricular late potentials</td>
<td>5.8 (2.2–15.9)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Left ventricular ejection fraction ≥40% and &lt;45%</td>
<td>1.7 (0.6–4.7)</td>
<td>0.34</td>
</tr>
<tr>
<td>Age ≥70 yrs</td>
<td>0.4 (0.1–1.8)</td>
<td>0.24</td>
</tr>
<tr>
<td>Men</td>
<td>0.5 (0.2–2.1)</td>
<td>0.17</td>
</tr>
<tr>
<td>Anterior wall infarction</td>
<td>0.9 (0.4–2.6)</td>
<td>0.99</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>0.3 (0.1–0.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td>2.3 (0.5–9.9)</td>
<td>0.27</td>
</tr>
<tr>
<td>Antiarrhythmic drugs</td>
<td>2.2 (0.6–7.7)</td>
<td>0.21</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>0.5 (0.1–2.0)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

CI = confidence interval.
analysis of 2 published clinical trials, Hohnloser et al. (9) reported that a negative microvolt TWA test is a useful marker in identifying patients at low risk of serious arrhythmic events among patients with prior MI and a reduced LVEF ≤30% (i.e., the MADIT II selection criteria). Recently, 2 prospective studies by Bloomfield et al. (10,11) demonstrated that an “abnormal” microvolt TWA test is a strong predictor of all-cause mortality and that a negative microvolt TWA test identifies a low-risk group not likely to benefit from ICD therapy in population with an LVEF ≤30% or ≤40%. In patient populations with severely reduced LVEF, the incidence of indeterminate test results on microvolt TWA is higher because of the occurrence of frequent extrasystoles or failure to achieve a heart rate of >105 beats/min with exercise, allowing positive and indeterminate microvolt TWA test outcomes to be combined as a single “abnormal category.” No studies have demonstrated the predictive significance of microvolt TWA with respect to serious arrhythmic events in the setting of preserved cardiac function after acute MI. The present prospective study suggests that a positive microvolt TWA test is an independent predictor of serious arrhythmic events. In identifying patients who need an ICD, further assessments may be necessary because of the low positive predictive value (9%). Microvolt TWA could be used in the primary screening of patients for sudden cardiac death in this patient population because both the sensitivity and negative predictive value of microvolt TWA were high (81% and 99.6%, respectively). In addition, an indeterminate microvolt TWA test may not be useful as a marker of an adverse outcome in this low-risk population because it was not associated with arrhythmic events. Risk stratification may differ between patients with reduced LVEF and those with preserved LVEF.

In patients with a reduced LV function, electrophysiologic testing may be a tool in identifying patients who would benefit from implantation of an ICD, as shown in previous studies (25). However, electrophysiologic testing is invasive, done in a hospital setting, and expensive. Its prognostic power is unknown in the setting of acute MI and an LVEF ≥40%. Although the positive predictive value of a positive microvolt TWA test is poor, its value could be improved when the test is combined with other noninvasive markers, such as NSVT and ventricular LP (8). Therefore,

Table 3. Predictive Values of Positive Microvolt T-Wave Alternans, Nonsustained Ventricular Tachycardia, and Ventricular Late Potentials Risk Variables With Serious Arrhythmic Events

<table>
<thead>
<tr>
<th>Risk Variable</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microvolt T-wave alternans</td>
<td>15/18 (83)</td>
<td>744/898 (83)</td>
<td>15/169 (9)</td>
<td>744/747 (99.6)</td>
<td>759/916 (83)</td>
</tr>
<tr>
<td>Nonsustained ventricular tachycardia</td>
<td>8/18 (44)</td>
<td>832/936 (83)</td>
<td>8/112 (7)</td>
<td>832/842 (98.8)</td>
<td>840/954 (88)</td>
</tr>
<tr>
<td>Ventricular late potentials</td>
<td>6/17 (35)</td>
<td>796/871 (91)</td>
<td>6/81 (7)</td>
<td>796/807 (98.6)</td>
<td>802/888 (90)</td>
</tr>
</tbody>
</table>

In Patients Without Class I Antiarrhythmic Drugs

<table>
<thead>
<tr>
<th>Risk Variable</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microvolt T-wave alternans</td>
<td>13/16 (81)</td>
<td>701/844 (83)</td>
<td>13/156 (8)</td>
<td>701/707 (99.6)</td>
<td>714/860 (83)</td>
</tr>
</tbody>
</table>

Values expressed as number of patients (%).
NPV = negative predictive value; PA = predictive accuracy; PPV = positive predictive value.
electrophysiologic testing may not be necessary to further stratify patients in this low-risk population.

**Study limitations.** Because of the limited scope of our study, we did not include autonomic imbalance markers such as heart-rate variability (26,27), baroreflex sensitivity (26), and heart rate turbulence (28) in our risk variables, which would be associated with serious arrhythmic events. So we do not know their utility in the detection of serious arrhythmic events in post-MI patients with preserved cardiac function.

The clinical outcome of patients may be influenced by the accompanying post-MI therapy. The low rate of beta-blocker use may influence the observed results in terms of risk stratification. In Western countries, beta-blockers are considered an obligatory mainstay of post-MI therapy with highly beneficial impact on prognosis. In Japan, beta-blocker use is remarkably low (21% in the present study). There are some reasons. In Japanese patients, coronary spasm plays an important role in the pathogenesis not only of variant angina but also acute coronary syndrome (29).

Pristipino et al. (30) have reported that Japanese patients exhibited a 3-fold–greater incidence than Caucasian patients of coronary spasm after acetylcholine. The Japanese guidelines for diagnosis and treatment of cardiovascular disease have stated that a physician may not use beta-blockers when coronary spasm was suspected as the cause of acute coronary syndrome (31). Therefore, the results of the present study may not necessarily be transferable to post-MI cohorts in Western countries.

**Conclusions.** In the revascularization treatment era, the incidence of arrhythmic death is very low among post-MI patients with preserved cardiac function. This prospective study reveals that a positive microvolt TWA test is associated with arrhythmic events and the incidence of indeterminate results of microvolt TWA is low in the setting of acute MI and an LVEF ≥40%. Although a positive microvolt TWA test could be used for risk stratification in this low-risk population, further assessments may be necessary for the selection of patients who need an ICD because of the low positive predictive value.

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**REFERENCES**