Determinant of Microvolt-Level T-Wave Alternans in Patients With Dilated Cardiomyopathy

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OBJECTIVES
The aim of this study was to clarify the clinical significance and the determinant of microvolt-level T-wave alternans (TWA) in patients with dilated cardiomyopathy (DCM).

BACKGROUND
The prevention of sudden death in patients with DCM remains the therapeutic target. T-wave alternans has been proposed as a powerful tool for identification of patients at high risk for ventricular arrhythmias and sudden death in coronary artery disease.

METHODS
In 58 DCM patients, TWA was measured during bicycle exercise testing using a CH 2000 system (Cambridge Heart, Bedford, Massachusetts). The New York Heart Association class, signal-averaged electrocardiogram, QT dispersion, left ventricular end-diastolic diameter (LVDD) and percent fractional shortening detected by echocardiogram and the grade of the ventricular arrhythmia were obtained in all patients.

RESULTS
T-wave alternans was positive in 23 patients (TWA+ group), negative in 25 (TWA− group) and indeterminate in 10. Univariate analysis showed that the percentage of patients with ventricular tachycardia (VT) and the LVDD in the TWA+ group was significantly higher than those in the TWA− group (61% vs. 8%, p < 0.001 and 65 ± 11 mm vs. 58 ± 8 mm, p < 0.05, respectively). The sensitivity, specificity and predictive accuracy of TWA for VT were 88%, 72% and 77%, respectively. Multivariate analysis showed that the presence of VT was a major independent determinant of TWA in patients with DCM (p = 0.003).

CONCLUSIONS
T-wave alternans was closely related to VT in patients with DCM. T-wave alternans is a useful noninvasive test for identifying high risk patients with DCM who have VT. (J Am Coll Cardiol 1999;34:374–80) © 1999 by the American College of Cardiology

Dilated cardiomyopathy (DCM) has traditionally been considered to be a disease with a severe prognosis often leading to sudden death or death from deteriorating congestive heart failure. The addition of angiotensin-converting enzyme inhibitor to the conventional therapy significantly reduced the mortality and hospitalization in patients with congestive heart failure (1). However, the prevention of sudden death in patients with DCM remains the therapeutic target. To identify patients at high risk for sudden death with noninvasive testing, signal-averaged electrocardiogram (SAECG), QT dispersion (QTd), exercise testing, heart rate variability and echocardiography have been used. However, there has been no powerful noninvasive test for identifying patients at high risk for sudden death in patients with DCM (2–9). In recent years, microvolt-level T-wave alternans (TWA) has been proposed as a powerful examination tool for the identification of patients at high risk for ventricular arrhythmias and sudden death in coronary artery disease. However, the clinical significance of TWA in patients with DCM has been unknown. The aim of this study was to clarify the clinical significance and the determinant of TWA in patients with DCM.

METHODS
Patients. The study population consisted of 58 consecutive patients with DCM who were referred to the Kobe University School of Medicine Hospital. The clinical diagnosis of nonischemic dilated cardiomyopathy was made according to the criteria recommended by the World Health Organization and the National Heart, Lung and Blood Institute (10,11). The clinical characteristics of the 58 study patients with DCM are summarized in Table 1. All patients underwent noninvasive and invasive evaluation including a physical examination, 12-lead electrocardiogram, chest radiography, M-mode and two-dimensional Doppler echocardiography, 24-h Holter monitoring, exercise stress test-

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ing, diagnostic right and left cardiac catheterization with coronary angiography and left ventriculography. All clinical testing was performed within three weeks except for coronary angiography and left ventriculography. Ventricular tachycardia (VT) was defined as ≥3 consecutive ventricular ectopic beats. If VT lasted for ≥30 s, it was defined as sustained VT. Patients were excluded if exercise was not possible (for example, because of joint pain), if atrial fibrillation was present or if a permanent pacemaker had previously been implanted. Ten patients with indeterminate TWA were excluded from the comparison of clinical parameters in this study, and a total of 48 patients with DCM was studied.

Measurements of TWA. The purpose of the study was explained to all participants, who gave their consent. T-wave alternans was measured at rest and during controlled bicycle exercise testing using a CH 2000 system (Cambridge Heart, Bedford, Massachusetts). This system used the spectral method described by Smith et al. (12). We performed TWA testing as described by Rosenbaum et al. (13,14). The alternans analysis was performed blind to all clinical data. The following were the positivity and negativity criteria for an alternans test. If there was a sustained positivity or negativity criteria, the record was considered positive if: 1) filtered QRS duration was >110 ms and 2) RMS 40 was <20 μV or LAS 40 was >38 ms at 40-Hz filtering. In patients with a wide QRS complex (QRS >110 ms), the SAECG was considered to be positive if two or three of the following criteria were positive: 1) filtered QRS duration was >145 ms; 2) RMS 40 was <17 μV; and 3) LAS 40 was >45 ms at 40-Hz filtering (6,17,18).

Measurements of QT dispersion. Standard electrocardiograms with simultaneous 12-lead acquisition were recorded at a paper speed of 25 mm/s. The investigator was blinded with respect to the patient profile. Patients with a wide QRS complex (QRS >110 ms, i.e., bundle branch block) were excluded from the assessment of ventricular repolarization using the QT interval. QT intervals were measured manually with calipers in a blinded fashion from the onset of the QRS complex to the end of the T wave, defined as the return to the TP baseline. When U waves were present, the QT interval was measured to the nadir of the curve between the T and U waves. If the end of the T wave could not be identified, the lead was not included. A minimum of eight leads in which the QT interval could be measured was required for the QTd to be determined. The QTd was defined as the difference between the longest and shortest QT intervals.

Statistical analysis. Data were expressed as mean ± SD. Univariate analysis was performed by unpaired t tests and chi-square tests between patients in the TWA-positive group and those in the TWA-negative group. A p value <0.05 was considered significant. Logistic regression analysis was performed using TWA as a response variable and six variables (New York Heart Association [NYHA] class, left ventricular end-diastolic diameter [LVDd], percent fractional shortening [%FS], QTd, SAECG and VT) as explanatory variables. Furthermore, a variable selection was performed using a forward stepwise method. We used six explanatory variables as candidate variables. Significant

### Table 1. Clinical Characteristics

<table>
<thead>
<tr>
<th>n</th>
<th>58</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>52 ± 14</td>
</tr>
<tr>
<td>Gender (n)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>49</td>
</tr>
<tr>
<td>Female</td>
<td>9</td>
</tr>
<tr>
<td>NYHA</td>
<td>1.6 ± 0.8</td>
</tr>
<tr>
<td>BP (mm Hg)</td>
<td></td>
</tr>
<tr>
<td>Systole</td>
<td>123 ± 19</td>
</tr>
<tr>
<td>Diastole</td>
<td>75 ± 11</td>
</tr>
<tr>
<td>CTR (%)</td>
<td>52 ± 7</td>
</tr>
</tbody>
</table>

Data presented are mean value ± SD or the number of subjects. BP = blood pressure; CTR = cardiothoracic ratio; NYHA = New York Heart Association class.
factors detected by univariate analysis were reassessed by a forward stepwise logistic regression analysis with values for inclusion and elimination set at $p = 0.05$ and $p = 0.10$, respectively. The results of the logistic regression analysis were presented as estimated odds ratios. A value of $p < 0.05$ was considered to be statistically significant. Data processing and analysis were performed with the Statistical Package for the Social Science Program (SPSS, Chicago, Illinois).

RESULTS

T-wave alternans. Fifty-eight patients with DCM were enrolled into the study. T-wave alternans was positive in 23 patients (40%), negative in 25 (43%) and indeterminate in 10 (17%). A representative example of a positive TWA is shown in Figure 1. Ten patients with indeterminate TWA were excluded from further evaluation. There were 39 men (81%) and 9 women (19%) (mean age 49 ± 13 years, range 25 to 69) in the study. There was no significant difference between patients with and without TWA in age, gender, NYHA classification, %FS, QTd or SAECG (Table 2, Fig. 2). The patient-specific heart rate threshold for the detection of TWA was 97 ± 11 beats/min in patients with TWA.

New York Heart Association classification. The NYHA classification was 1.7 ± 1.0 in patients with TWA and 1.4 ± 0.7 in patients without TWA ($p = NS$) (Table 2).
Echocardiography. The LVDd was 65 ± 11 ms in patients with TWA and 58 ± 8 ms in patients without TWA. This difference reached statistical significance (p < 0.05). The %FS was 18 ± 7% in patients with TWA and 21 ± 6% in patients without TWA (p = NS) (Fig. 2).

QT dispersion. There were 15 patients with TWA with a normal QRS complex, and 22 patients without TWA with a normal QRS complex. In patients with TWA with a normal QRS complex, QTd was 74 ± 25 ms, and in patients without TWA with a normal QRS complex, QTd was 64 ± 16 ms (p = NS) (Fig. 2). The sensitivity, specificity and predictive accuracy of an increased QTd (QTd > 100 ms) for VT were 30%, 100% and 80%, respectively.

Signal-averaged electrocardiogram. The SAECG was positive in 12 patients. The SAECG was positive in eight patients with TWA (35%), compared with only four patients without TWA (16%) (p = NS) (Fig. 3). The filtered QRS was 137 ± 31 ms in patients with TWA and 118 ± 20 ms in patients without TWA (p = NS). The RMS 40 was 43 ± 39 μV in patients with TWA and 30 ± 19 μV in patients without TWA (p = NS). The LAS 40 was 30 ± 10 ms in patients with TWA and 33 ± 7 μV in patients without TWA (p = NS). All patients with DCM had an abnormal filtered QRS. Of 16 patients with VT, the SAECG was positive in 5 patients (31%) and of 32 patients without VT, it was positive in 7 patients (22%) (p = NS).

Table 2. Clinical Characteristics in Patients With or Without TWA

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Age (yr)</th>
<th>Gender (M/F)</th>
<th>NYHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>TWA+</td>
<td>23</td>
<td>50 ± 13</td>
<td>20/3</td>
<td>1.7 ± 1.0</td>
</tr>
<tr>
<td>TWA−</td>
<td>25</td>
<td>49 ± 15</td>
<td>19/6</td>
<td>1.4 ± 0.7</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data presented are mean value ± SD. NYHA = New York Heart Association class; TWA = T-wave alternans.

DISCUSSION

The problem of sudden cardiac death in patients with DCM. Dilated cardiomyopathy is a primary disease of the heart muscle usually involving the dilation of all four chambers but principally the left ventricle. The prognosis for patients afflicted with DCM has been poor, with a high mortality rate of 25% to 50% in the first two years after diagnosis (3,4,19). Furthermore, approximately half of these deaths occur suddenly and unexpectedly (3,20). Therefore, from a public health viewpoint, identification and treatment of high risk patients before they experience a major arrhythmic event is expected to have the greatest effect on the problem of sudden cardiac death. Unfortunately, current attempts to risk-stratify patients further with noninvasive testing such as echocardiography, SAECG, heart rate variability and QTd have had limited success (2–9,21). The present study showed that neither the SAECG nor QTd

Holter monitoring. Ventricular tachycardia was present in 16 out of 48 patients with DCM by 24-h Holter monitoring. Two patients had sustained VT and one patient had ventricular fibrillation (VF). Ventricular tachycardia was present in 14 patients with TWA (61%) and 2 patients without TWA (8%) (p < 0.001) (Fig. 3). Three patients with sustained VT/VF were all TWA positive. The sensitivity, specificity and predictive accuracy of TWA for VT were 88%, 72% and 77%, respectively. The specificity of TWA for VT was inferior to that of the QTd and SAECG, but the sensitivity of TWA for VT was superior to that of the QTd and SAECG. Univariate analysis showed that LVDd and VT were significantly related to TWA in patients with DCM. Multiple logistic regression analysis using a forward stepwise method showed that VT was a major independent determinant of TWA (odds ratio = 4.00; p = 0.003) in patients with DCM (Table 3).

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The sensitivity, specificity and predictive accuracy of the SAECG for VT were 31%, 78% and 63%, respectively.

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Figure 2. The left ventricular end-diastolic diameter (LVDd) in patients with T-wave alternans (TWA) was significantly larger than that in patients without TWA (p < 0.05). No significant difference was observed in the percent fractional shortening (%FS) and QT dispersion (QTd) between the two groups.
were useful for risk stratification in the setting of DCM, because of their low sensitivity for VT. This is consistent with the results of the previous studies by Keeling et al. (9), Turitto et al. (22) and Grimm et al. (6,7,23). The prognostic value of the SAECG in DCM was reported to be inferior to that in old myocardial infarction (21). However, studies that have evaluated the prognostic value of the SAECG in patients with DCM are not conclusive. Mancini et al. (24) reported that an abnormal SAECG was a marker of past and future arrhythmic events in patients with nonischemic cardiomyopathy. The discrepancies between the study by Mancini et al. and the present study may, in part, be due to the differences in methods. Patients with a wide QRS complex were excluded from analysis in the study by Mancini et al. (24), whereas in this study patients with wide QRS complex were included. Furthermore, it has been more difficult to predict which patients might be at high risk for arrhythmic sudden death.

T-wave alternans in patients with ischemic heart disease and cardiomyopathies. In recent years, the presence of subtle and visually inapparent beat-to-beat alternation in the T-wave amplitude has been recognized as a harbinger of life-threatening ventricular arrhythmias. Smith et al. first reported a spectral method to measure microvolt-level TWA and demonstrated a strong correlation between such TWA and the extent of the decrease in the VF threshold caused by hypothermia or coronary artery ligation in dogs (12). In 1994, Rosenbaum et al. (14) documented a highly significant relationship between microvolt-level TWA on the electrocardiogram during atrial pacing measured with a CH2000 system and inducible sustained VT/VF as well as arrhythmia-free survival in 83 patients with mainly coronary artery disease. Murda’h et al. (25) reported that TWA was correlated with the presence of clinical risk factors, such as family history of sudden death, recurrent unexplained syncope, nonsustained VT on Holter monitoring and a flat blood pressure response on treadmill exercise ($p < 0.005$) in patients with hypertrophic cardiomyopathy (HCM). They also reported that TWA might be an important marker for sustained VT/VF in patients with HCM, because five patients with documented VT/VF were all TWA positive. Momiyama et al. reported that TWA might be a useful marker for ventricular arrhythmic risk in patients with HCM (26). However, there were no reports in terms of the significance of TWA in patients with DCM. Our present study is the first to investigate the relationship between TWA and risk stratification in patients with DCM by controlled bicycle exercise testing using a CH2000 system. The results of our study demonstrated that there was no significant difference in the NYHA class, %FS, SAECG or QTd between patients with and those without TWA. The percentage of patients with VT was significantly higher in patients with TWA than those without TWA, and the LVDd on M-mode and two-dimensional Doppler echocardiography was also significantly larger in patients with TWA than those without TWA. Multivariate analysis showed that VT was a major independent determinant of TWA in patients with DCM. The results of this study suggest that TWA may be helpful in identifying patients with DCM who have VT. Hofmann et al. (3) reported that left ventricular ejection fraction, cardiac index and ventricular arrhythmias were independent predictors of cardiac death in patients with DCM. Maria et al. (27) reported that the severity of ventricular arrhythmias was a major independent predictor of the prognosis in patients with DCM. In patients with mild to moderate heart failure, VT frequency recorded on Holter monitoring was independently associated with both total mortality and sudden death (14). Therefore, TWA was useful for identifying the risk stratification in the setting of DCM, because of its high sensitivity for VT. The SAECG and QTd had a high specificity for VT, but a low sensitivity for VT in patients with DCM. The predictive value of TWA for VT was superior to that of the SAECG and QTd.

TWA in Patients With DCM

**Table 3.** Univariate and Multivariate Analysis: Determinant of TWA

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Univariate Analysis, $p$</th>
<th>OR</th>
<th>Multivariate Analysis* $p$</th>
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<tbody>
<tr>
<td>NYHA</td>
<td>0.124</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LVDd</td>
<td>0.023</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>%FS</td>
<td>0.085</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>QTd</td>
<td>0.095</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>SAECG</td>
<td>0.265</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>VT</td>
<td>$&lt;0.001$</td>
<td>4.0</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*Logistic regression analysis using forward stepwise method. %FS = percent fractional shortening; LVDd = left ventricular end-diastolic diameter; NYHA = New York Heart Association class; OR = odds ratio; QTd = QT dispersion; SAECG = signal-averaged electrocardiogram; TWA = T-wave alternans; VT = ventricular tachycardia.
The mechanisms of TWA. In patients with coronary artery disease, TWA has been reported to be closely related to sustained VT/VF (14). In patients with DCM, TWA was closely related with more than three consecutive beats of premature ventricular contractions in the present study. This difference could be due to patients with coronary artery disease having a partial relatively damaged area of the myocardium equivalent to obstructive coronary artery circulation, whereas patients with DCM have a large diffuse area of damaged myocardium. The mechanism of VT after myocardial infarction is reentry through the infarct region (28). On the other hand, the mechanisms and precise electrophysiologic characteristics of VT in patients with DCM are unclear; in addition, several factors may generate ventricular arrhythmias in DCM. These include fibrosis leading to uncoupling of cells, ventricular hypertrophy, increase in cytosolic calcium, subendocardial ischemia, electrolyte disturbances and others. Therefore, the cause of sudden cardiac death in DCM may be multifactorial (29).

The proposed mechanisms for alternans-related arrhythmogenesis have been discussed previously. Two basic mechanisms have been hypothesized. One mechanism is a population mechanism, the other one is a cellular mechanism. It is not known whether either one of these two mechanisms actually pertains to alternans-related arrhythmogenesis in man (13,30).

Study limitations. Several important factors must be considered in interpreting our results. Many of the patients with DCM had atrial fibrillation or frequent ectopic beats, or were pacemaker dependent. They must be excluded from the study population because their electrocardiograms could not be analyzed with the spectral method. In the present study, 17% of patients with DCM were indeterminate for TWA because of a high noise level with motion artifact or baseline instability. This difference could be due to patients with coronary artery disease having a partial relatively damaged area of the myocardium equivalent to obstructive coronary artery circulation, whereas patients with DCM have a large diffuse area of damaged myocardium. The mechanism of VT after myocardial infarction is reentry through the infarct region (28). On the other hand, the mechanisms and precise electrophysiologic characteristics of VT in patients with DCM are unclear; in addition, several factors may generate ventricular arrhythmias in DCM. These include fibrosis leading to uncoupling of cells, ventricular hypertrophy, increase in cytosolic calcium, subendocardial ischemia, electrolyte disturbances and others. Therefore, the cause of sudden cardiac death in DCM may be multifactorial (29).

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Conclusions. Our results suggest that microvolt-level TWA was closely related to ventricular tachycardia in patients with DCM. T-wave alternans may be a useful noninvasive tool for identifying high risk patients with DCM who have VT. The independent determinant of TWA in patients with DCM was VT.

References