Risk Stratification for Sudden Cardiac Death in Dilated Cardiomyopathy Using Microvolt-Level T-Wave Alternans

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Predicting sudden cardiac death (SCD) in patients with dilated cardiomyopathy (DCM) is difficult, so the present study evaluated the efficacy of microvolt-level T-wave alternans (TWA) and compared it with conventional parameters for prospective risk stratification of SCD in patients with DCM. Eighty-two patients with DCM (53±15 years old, 67 M/15 F) underwent assessment of TWA, left ventricular end-diastolic diameter (LVDd), left ventricular ejection fraction (LVEF), signal-averaged ECG, and analysis of 24-h Holter monitoring and QT dispersion (QTd). The endpoint of the study was defined as either SCD or documented sustained ventricular tachycardia/ventricular fibrillation (VT/VF) during the follow-up period. During an average follow-up period of 24 months, 1 patient died suddenly and 9 patients had VT/VF. Kaplan-Meier survival analysis showed that TWA, LVEF (≤35%), nonsustained ventricular tachycardia, and QTd (>90 ms) were significant univariate risk stratifiers (p<0.005, p=0.005, p=0.005, and p=0.05, respectively). Multivariate Cox regression analysis showed that TWA and the LVEF were statistically significant independent risk stratifiers (p<0.05 and p<0.01, respectively).

A combination of TWA and LVEF identified high risk DCM patients (p<0.01); TWA for the electrical substrate and the LVEF for the hemodynamic function. (Jpn Circ J 2001; 65: 76–80)

Key Words: Dilated cardiomyopathy; Left ventricular ejection fraction; Risk stratification; Sudden cardiac death; T-wave alternans

Dilated cardiomyopathy (DCM) is characterized by dilatation and impaired contraction of either the left ventricle or both ventricles. Presentation is usually with heart failure, which is often progressive. Arrhythmias, thromboembolism, and sudden death are common and may occur at any stage.1 The median survival period of patients with DCM has been reported to be approximately 2 years, with a 5-year-survival rate of approximately 50%;2 and of these deaths approximately 50% are sudden and unexpected.3 The therapeutic strategy for DCM has dramatically changed; angiotensin-converting-enzyme inhibitors (ACEI), β-blockers, and amiodarone have improved survival in patients with congestive heart failure, and implantable cardioverter defibrillators (ICD) have significantly reduced the mortality in patients with sudden cardiac death (SCD).4,5 The indication for ICD therapy is documented spontaneous or induced ventricular tachycardia/ventricular fibrillation (VT/VF) but some patients with sustained VT/VF (SVT/VF) with their first attack, so the identification of these high-risk patients before they experience a major arrhythmic event will have the greatest impact on the rate of SCD. It has been recently reported that microvolt-level T-wave alternans (TWA) can be detected with newly developed equipment using a spectral method, and that the presence of such subtle alternans is predictive of spontaneous and inducible VT/VF in patients with ischemic heart disease.6 However, the use of TWA as a predictor for arrhythmogenesis together with the conventional risk stratification methods in patients with DCM remains unknown. We previously reported that the determinant of TWA was nonsustained VT (NSVT) on Holter monitoring in patients with DCM,7 so the present study evaluated TWA as a new predictor for arrhythmogenesis and prospectively compared it with conventional parameters for risk stratification of SCD in patients with DCM.

Methods

Patient Population

The study population consisted of 82 consecutive patients with DCM who were referred to the Kobe University School of Medicine Hospital between February 1997 and April 2000. The clinical diagnosis of nonischemic DCM was made according to the criteria recommended by the World Health Organization and the National Heart, Lung and Blood Institute. All patients underwent both noninvasive and invasive evaluation, including a physical examination, 12-lead ECG, chest radiography, M-mode and 2-dimensional Doppler echocardiography, 24-h Holter monitoring, exercise stress testing, diagnostic cardiac catheterization with coronary angiography and left ventriculography. All patients were taken off their antiarrhythmic treatment. Patients were excluded if atrial fibrillation was present or if a permanent pacemaker had previously been implanted. The aim of the study was explained to all the subjects and informed consent was obtained.

Measurement of TWA

TWA was measured at rest and during controlled bicycle exercise testing using a CH 2000 system (Cambridge Heart, Inc, Bedford, MA, USA) as previously described. The
alternans analysis was performed blind to all clinical data. TWA was prospectively defined to be positive when it was sustained with alternans voltage ≥1.9 μV during exercise with an onset heart rate ≤110 beats/min, or 1.0 μV at rest for a period of at least 1 min, provided that the alternans ratio was ≥3. TWA was prospectively defined to be indeterminate if the criteria for artifact-free data was available while the heart rate was maintained at a level ≥105 beats/min. Otherwise, TWA was defined to be indeterminant.10,11,14–16

**Measurements of Conventional Risk Markers**

The left ventricular end-diastolic diameter (LVDd) and the left ventricular ejection fraction (LVEF) were calculated from M-mode and 2-dimensional Doppler echocardiography. A prospectively defined cut-point of an LVEF ≤35% was used to define the high risk group.1 Patients underwent 24-h ambulatory monitoring during normal daily activities. NSVT was defined as the documentation of ≥3 consecutive ventricular ectopic beats at a rate of ≥100 beats/min. The patients underwent signal-averaged electrocardiogram (SAECG) recording. Orthogonal bipolar X, Y, and Z leads were recorded until a noise level of 0.4 μV was reached using the standard techniques (FUKUDA DENSHTI FDX-6521, Tokyo, Japan). Standard ECGs with simultaneous 12-lead acquisition were recorded at a paper speed of 25 mm/s to analyze the QT dispersion (QTd). The criteria for abnormality of the SAECG and the measurement of the QT intervals were defined as previously described.1 The QTd was defined as the difference between the maximum and minimum QT interval across all 12 ECG leads. The QTd was deemed indeterminate if there were frequent ventricular ectopic beats. A prospectively defined cut-point of a QTd >90 ms was used to define the high risk group.18,19

**Endpoint of Follow-up**

The end point of this study was prospectively defined as SCD, documented SVT or resuscitated VF. Sudden death was defined as instantaneous, unexpected death or death within 1 h of symptom onset not related to circulatory failure. The SVT was defined as a documented tachycardia of ventricular origin at a rate of ≥30 s or resulting in hemodynamic collapse.

**Statistical Analysis**

Data were expressed as mean ± SD. A chi-square test was used to compare categorical variables. The unpaired Student’s t test was used to compare continuous variables. The cumulative probability of events was determined by the Kaplan-Meier method, and differences in the distribution of events were evaluated with the log rank test. Significant factors detected by univariate analysis were reassessed by multivariate analysis. Multivariate analysis was performed by means of a Cox regression analysis. Statistical significance was considered at a value of p<0.05.

**Results**

**Patient Characteristics**

Eighty-two DCM patients (15 women, 67 men; mean age, 53±15 years) entered the study (Table 1), at the beginning of which 56 (68%) were taking ACEI and 40 (49%) were taking β-blockers. Eighteen patients were excluded because of poor ECG recordings with noise or frequent ectopic beats, so the follow-up analysis comprised 64 patients.

**Events During Follow-up**

During an average follow-up duration of 24±13 months, 10 patients experienced arrhythmic events: 1 patient died suddenly and 9 patients had SVT/VF.

**Results of TWA**

TWA was positive in 30 patients (37%), negative in 34 (41%), and indeterminate in 18 (22%) who were subsequently excluded from further evaluation. The percentage of patients with TWA in the arrhythmic events group (group A) was significantly larger than that in the nonevent group (group B) (90% vs 39%, p<0.005) (Table 2). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of TWA for arrhythmic events were 90%, 61%, 30%, and 97%, respectively (Table 3).

**Conclusions of Risk Markers**

The LVDd in group A was 66±6 mm and 60±10 mm in group B (p=NS) (Table 2). The LVEF in group A was 34±13% and 47±13% in group B (p<0.01) (Table 2). The percentage of patients with NSVT in group A was signifi-
significantly larger than that in group B (80% vs 33%, p<0.05) (Table 2). The SAECG was positive in 4 patients in group A, compared with 11 patients in group B (40% vs 20%, p=NS) (Table 2). The QTd in group A was 76±33 ms and 67±18 ms in group B (p=NS) (Table 2). The sensitivity, specificity, PPV, and NPV of the LVDD, LVEF, NSVT, SAECG, and QTd for arrhythmic events are shown in Table 3.

### Prediction of Event-Free Survival

#### Using a Single Variable Model

Kaplan-Meier actual survival analysis was used to ascertain the ability of the 6 risk stratifiers (TWA, LVDD, LVEF, NSVT, SAECG, and QTd) to predict event-free survival. Univariate Kaplan-Meier survival analysis revealed that TWA (Fig 1), LVEF (Fig 2), NSVT, and QTd were statistically significant according to the log rank test (p<0.005, p<0.005, p<0.005, and p<0.05, respectively). The significant factors detected by univariate analysis were then assessed by multivariate analysis. Using the Cox proportional hazard model, TWA and the LVEF were found to be statistically significant predictors of 37 months event-free survival (p<0.05 and p<0.01, respectively).

#### Prediction of Event-Free Survival With Two Variable Model

<table>
<thead>
<tr>
<th>LVEF ≤35% NSVT(+)</th>
<th>Se (%)</th>
<th>Sp (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>RR</th>
<th>p value (χ² test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF ≤35% SAECG(+)</td>
<td>50</td>
<td>85</td>
<td>38</td>
<td>90</td>
<td>3.92</td>
<td>0.0111</td>
</tr>
<tr>
<td>LVEF ≤35% QTd &gt;90ms</td>
<td>20</td>
<td>96</td>
<td>50</td>
<td>87</td>
<td>3.75</td>
<td>0.0405</td>
</tr>
<tr>
<td>LVEF ≤35% TWA(+)</td>
<td>60</td>
<td>85</td>
<td>43</td>
<td>92</td>
<td>5.36</td>
<td>0.0015</td>
</tr>
</tbody>
</table>

Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; RR, relative risk; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; SAECG, signal-averaged ECG; QTd, QT dispersion.

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**Table 3**: TWA and Conventional Risk Markers as Predictors for Event-Free Survival

<table>
<thead>
<tr>
<th>TWA</th>
<th>Se (%)</th>
<th>Sp (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>RR</th>
<th>p value (χ² test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TWA</td>
<td>90</td>
<td>61</td>
<td>30</td>
<td>97</td>
<td>10.2</td>
<td>0.0029</td>
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<tr>
<td>LVDD</td>
<td>30</td>
<td>85</td>
<td>27</td>
<td>87</td>
<td>2.06</td>
<td>0.2423</td>
</tr>
<tr>
<td>LVEF</td>
<td>70</td>
<td>80</td>
<td>39</td>
<td>93</td>
<td>5.96</td>
<td>0.0013</td>
</tr>
<tr>
<td>NSVT</td>
<td>80</td>
<td>67</td>
<td>31</td>
<td>95</td>
<td>5.85</td>
<td>0.0053</td>
</tr>
<tr>
<td>SAECG</td>
<td>40</td>
<td>80</td>
<td>27</td>
<td>88</td>
<td>2.18</td>
<td>0.1783</td>
</tr>
<tr>
<td>QTd</td>
<td>40</td>
<td>91</td>
<td>44</td>
<td>89</td>
<td>4.07</td>
<td>0.0102</td>
</tr>
</tbody>
</table>

Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; RR, relative risk; TWA, T-wave alternans; LVDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; SAECG, signal-averaged ECG; QTd, QT dispersion.

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**Table 4**: Prediction of Event-Free Survival With Two Variable Model

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Fig 1. Kaplan-Meier survival curves of patients with positive/negative TWA.

Fig 2. Kaplan-Meier survival curves of patients with LVEF ≤35% / LVEF >35%.

Fig 3. Kaplan-Meier survival curves of patients with LVEF ≤35%, positive TWA/not LVEF ≤35%, positive TWA.
Combination of Hemodynamic Function and Electrical Substrate

To evaluate risk stratification with a 2-variable model, we used the combination of the LVEF for the hemodynamic function with the TWA, NSVT, SAECG, and QTd for the electrical substrate. Kaplan-Meier survival analysis was used to ascertain the ability of 4 sets of 2-variable risk stratifiers (LVEF ≤ 35% with TWA+, LVEF ≤ 35% with NSVT+, LVEF ≤ 35% with SAECG+, and LVEF ≤ 35% with QTd > 90 ms). The specificity, sensitivity, PPV, and NPV of the 2-variable models for arrhythmic event are shown in Table 4. Multivariate Kaplan-Meier survival analysis revealed that the combinations of an LVEF ≤ 35% with TWA+ (Fig 3), LVEF ≤ 35% with NSVT+, and LVEF ≤ 35% with a QTd > 90 ms were statistically significant according to the log rank test (p < 0.005, p < 0.05, and p < 0.05, respectively). The significant factors detected by univariate analysis were reassessed by multivariate analysis. Multivariate Cox regression analysis revealed that the combination of an LVEF ≤ 35% with TWA+ was the only statistically significant independent risk factor (p < 0.01). None of the 30 patients with TWA+ and an LVEF > 35% experienced an arrhythmic event (p < 0.05); that is, the very low-risk patients with DCM.

Discussion

Main Findings

This is the first prospective study to investigate the clinical significance of TWA as a predictor of arrhythmogenesis and compare it with the conventional risk stratifiers for SCD in patients with DCM. Kaplan-Meier survival analysis showed that TWA, LVEF, NSVT, and QTd were significant univariate risk stratifiers in patients with DCM (p < 0.005, p < 0.005, p < 0.005, and p < 0.05, respectively), and that TWA was a sensitive predictor (Table 3). Multivariate Cox regression analysis showed that TWA and the LVEF were statistically significant independent risk stratifiers. The combination of TWA+ and an LVEF ≤ 35% identified high-risk patients with DCM (p < 0.01) (Table 4).

TWA and Conventional Risk Stratification Methods in Patients With DCM

The prognosis of patients with DCM is poor with a high mortality rate of 25–50% in the first 2 years following diagnosis. Approximately 50% of all deaths occur suddenly and unexpectedly as a result of rapid VT or VF. Therefore, the prevention of SCD in patients with DCM has been the therapeutic target. Electrophysiological (EP) testing has not been helpful in predicting the arrhythmic risk stratification in patients with DCM. EP testing is the standard procedure for risk stratification, but this procedure has not been helpful in predicting the DCM patients at high risk for SCD. Therefore, identification of these high-risk patients before they experience a major arrhythmic event will have the greatest impact on the problem of SCD in patients with DCM. The usefulness of the QTd for arrhythmic risk prediction was limited by the large overlap of the QTd between patients with and without arrhythmic events. Doval et al reported that couples and/or NSVT were even more predictive for SCD in patients with congestive heart failure (RR, 10.1; 95% CI, 1.91–52.7; p < 0.01). Wilson et al. reported a lack of a relationship between ventricular arrhythmias and sudden death in patients with chronic heart failure. In the present study, NSVT was a univariate risk stratifier and the discrepancy between these 2 studies may be the result of the difference in the medications. None of the patients were treated with ACEIs or β-blockers in the Wilson study.

Hofmann et al. demonstrated an association between frequent complex ventricular arrhythmias and a depressed LVEF, which identified patients who were at risk for sudden death. Similar to their results, we found the LVEF to be a statistically significant multivariate risk stratifier.

Fei et al. reported that HRV was significantly decreased in patients with congestive heart failure, but that it did not help with identifying those patients who were at increased risk for SCD. All these studies have shown that the LVEF is a significant risk stratifier in patients with DCM and the present study has revealed that TWA, as a new predictor for arrhythmogenesis, is a statistically significant multivariate risk stratifier in these patients, which is consistent with the results of a previous study by Rosenbaum et al. of ischemic heart disease.

Prophylactic ICD Implantation in Patients With DCM

From the viewpoint of public health, the prevention of SCD in patients with DCM has been the therapeutic target. In recent years, several prospective studies have shown improved survival with ICD therapy in patients at high risk for SCD because of VT/VF. The guidelines for implantation of ICDs are documented spontaneous or induced VT/VF. In patients with post myocardial infarction, invasive EP testing is the standard procedure for risk stratification, but this procedure has not been helpful in predicting the DCM patients at high risk for SCD. Therefore, identification of these high-risk patients before they experience a major arrhythmic event will have the greatest impact on the problem of SCD in patients with DCM. Therefore, identification of these high-risk patients before they experience a major arrhythmic event will have the greatest impact on the problem of SCD in patients with DCM. Therefore, identification of these high-risk patients before they experience a major arrhythmic event will have the greatest impact on the problem of SCD in patients with DCM. Therefore, identification of these high-risk patients before they experience a major arrhythmic event will have the greatest impact on the problem of SCD in patients with DCM. Therefore, identification of these high-risk patients before they experience a major arrhythmic event will have the greatest impact on the problem of SCD in patients with DCM. Therefore, identification of these high-risk patients before they experience a major arrhythmic event will have the greatest impact on the problem of SCD in patients with DCM. Therefore, identification of these high-risk patients before they experience a major arrhythmic event will have the greatest impact on the problem of SCD in patients with DCM.

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ing TWA and the hemodynamic function may be useful screening tests for the indication for ICD implantation in patients with DCM.

**Study Limitations**

One limitation was the small sample size, so we could not evaluate risk stratification in the subgroup of patients with an LVEF >35%. It is very important to identify those patients at high risk for SCD, but without left ventricular dysfunction. Secondly, many of the patients with DCM had atrial fibrillation, frequent ectopic beats or had a paced rhythm and so were excluded from analysis. Thirdly, SCD in patients with DCM is not always because of SVT/VF. Bradyarrhythmias and electromechanical dissociation may be a more frequent cause of SCD in nonischemic cardiomyopathies. Fourthly, the mechanism of TWA remains unclear. Although Pastore et al demonstrated that action potential alternans occurring discordantly in the myocardium causes dispersion of recovery that leads to reentrant ventricular fibrillation, further studies are required to fully clarify the exact mechanism of TWA.

**Conclusions**

TWA for the electrical substrate and the LVEF for the hemodynamic function are useful risk stratifiers for patients with DCM. This study suggests that analysis of TWA and determination of the LVEF are useful screening tests for determining the indication for ICD therapy, and thus lessening the risk of SCD, in patients with DCM.

**References**
