Comparison of T-Wave Alternans and QT interval Dispersion to Predict Ventricular Tachyarrhythmia in Patients with Dilated Cardiomyopathy and without Antiarrhythmic Drugs
A Prospective Study

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SUMMARY

Microvolt T-wave alternans (TWA) and QT interval dispersion (QTD), which reflect temporal and spatial repolarization abnormalities, respectively, have been proposed as useful indices to identify patients at risk for ventricular tachyarrhythmias (VTs). The purpose of this study was to clarify which repolarization abnormality marker is more useful in predicting arrhythmic events in patients with dilated cardiomyopathy (DCM).

Forty-two consecutive nonischemic DCM patients underwent the assessment of TWA and QTD. Patients undergoing antiarrhythmic pharmacotherapy, except β-blockers and those with irregular basic rhythms, were excluded from entry. Eight patients were also excluded because of indeterminate test results. Therefore, 34 DCM patients were prospectively assessed. The end point of the study was the documentation of VT defined as ≥5 consecutive ectopic beats during the follow-up period.

TWA and QTD (≥65 msec) were positive in 24 (80%) and 11 (37%) of 30 patients with available follow-up data, respectively. There was no relationship between TWA and QTD. During a follow-up of 13 ± 11 months, VTs occurred in 13 patients (43%). In Cox regression analysis, TWA was a significant risk stratifier (p = 0.02), whereas QTD was not. The sensitivity, specificity, and positive and negative predictive values of TWA in predicting VTs were 100%, 35%, 54%, and 100%, respectively.

TWA could be a useful noninvasive index to identify patients at risk for VTs in the setting of DCM. This study may suggest that temporal repolarization abnormality is associated more with arrhythmogenesis than with spatial repolarization abnormality in DCM patients. (Jpn Heart J 2001; 42: 451-457)

Key words: T-wave alternans, QT Dispersion, Dilated cardiomyopathy, Ventricular arrhythmia
VENTRICULAR arrhythmias have been associated with various factors. At present, repolarization inhomogeneity of ventricular myocardium is thought to be a factor in the pathogenesis of ventricular arrhythmias.\cite{1,2} Noninvasive markers, such as microvolt T-wave alternans (TWA) and QT interval dispersion (QTD), which reflect temporal and spatial repolarization abnormalities, respectively, have been proposed as useful indices to identify patients at risk of ventricular arrhythmias based on coronary artery disease.\cite{3-8} However, little information is available regarding the clinical significance of TWA and QTD in the setting of DCM.\cite{9-12} Moreover, these markers have not been prospectively compared to each other for patients with DCM. In the present study, we prospectively compared the clinical significance of TWA and QTD to identify patients at risk for ventricular tachyarrhythmias (VTs) in the setting of DCM.

**PATIENTS AND METHODS**

**Patient population:** We screened 68 consecutive patients with nonischemic DCM who were referred to Toho University Ohashi Hospital from February 1997 to April 2000. Patients were excluded from this study if their baseline rhythm was not a normal sinus rhythm. Patients undergoing antiarrhythmic pharmacotherapy other than β-blockers were also excluded from participation because antiarrhythmic drugs influence repolarization abnormalities. Although 42 patients underwent assessment for TWA and QTD, 8 patients with indeterminate test results were excluded from the study. Therefore, 34 patients were prospectively assessed. All of the patients gave informed consent prior to enrollment in this study. DCM patients were prospectively assessed for TWA and QTD. The characteristics of the 34 study subjects are shown in Table I. The study group con-

| Table I. Clinical Characteristics of the Study Population |
|-----------------|-----------------|
| No. of patients | 34              |
| Age (years)     | 53±16           |
| Gender          |                 |
| Men             | 31 (91%)        |
| Women           | 3 (9%)          |
| NYHA classification | 1.8±0.4   |
| LVEF (%)        | 33±15           |
| LEVDD (mm)      | 64±10           |
| β-blocker use   | 8 (24%)         |
| ACE inhibitor use | 34 (100%)     |

NYHA=New York Heart Association; LVEF=left ventricular ejection fraction; LEVDD=left ventricular end-diastolic diameter; ACE=angiotensin converting enzyme.
sisted of 3 women and 31 men with a mean age of 53±16 years. The mean New York Heart Association (NYHA) classification at the time of noninvasive assessment was 1.8±0.4. The mean left ventricular ejection fraction (LVEF) and left ventricular end-diastolic diameter (LVEDD) by left ventriculography were 33±15% and 64±10 mm, respectively. β-Blockers were administered to 8 patients. Angiotensin-converting enzyme inhibitors were used in all of the patients.

**Measurement of repolarization inhomogeneity markers:** Noninvasive measurements were carried out prospectively by investigators blinded to other clinical data.

**QT interval and dispersion.** Twelve-lead ECGs were recorded using a computerized ECG machine (FDX-6521, Fukuda Denshi Co., Tokyo) with newly developed software (QTD-1) for QT interval analysis. The QT intervals and corrected QT intervals (QTc) for each lead and QT dispersion were automatically calculated. In brief, the QT intervals were measured by averaging beats from similar cycles. A global QRS onset and t-wave offset are determined for all 12 leads, and then an individual QT interval is measured for each lead. When the t waves were too flat or U waves were present, these leads were manually excluded from analysis of the QT interval. The QT intervals were automatically corrected for heart rate with Bazett's formula. The QTD was defined as the difference in the minimum and maximum QTc for any of the 12 ECG leads in which it could be reliably determined. The QTD was considered positive when QTD ≥65 msec.

**T-Wave alternans.** After determining QTD and QTcD, TWA was measured during a supine bicycle exercise test using the CH2000 system (Cambridge Heart Inc., Bedford, MA, USA), as previously described. Standard 9 ECG leads (aVR, aVL, aVF, and V1-V6), and the Frank orthogonal (VM, X, Y, and Z) configuration were used. Microvolt t-wave alternans was measured using the spectral method. Alternans voltage and alternans ratio were computed from the beat domain power spectrum. The alternans voltage reflects the characteristic difference in mean t-wave amplitude. The alternans ratio normalizes alternans voltage with respect to background noise and provides a measure of the statistical significance of alternans voltage. The TWA was considered positive when the sustained alternans voltage was >1.9 µV with an alternans ratio >3.0 for any orthogonal lead or two adjacent pericordial leads during exercise with a heart rate onset below 70% of the predicted heart rate for at least 1 minute. TWA was considered negative when positive criteria were not met. Patients with indeterminate test results had already been excluded from the study.

**Follow-up and Study End Point:** All of the patients were followed as outpatients at our institute, as previously described. The end point of the study was prospectively defined as the first documentation of VT determined by standard ECG or 24-hour Holter ECG. VTs were defined as ≥5 consecutive ventricular ectopic
beats at a rate of $\geq 120$ beats/min. If VT lasted for $\geq 30$ sec, it was defined as sustained VTs. Patients undergoing antiarrhythmic pharmacotherapy or whose $\beta$-blocker use changed during the follow-up period were excluded from the prospective assessment.

**Statistical analysis:** Continuous data are expressed as mean±SD and were analyzed using Student's $t$ test. Comparisons between clinical variables were evaluated using a chi-square analysis. The association between TWA, QTD, and the occurrence of VT was evaluated with univariate Cox regression analysis. Predictive values for VTs were also assessed. Time to occurrence of VTs was estimated using the Kaplan-Meier method. A value of $p<0.05$ was considered statistically significant.

**RESULTS**

Four patients were excluded from the follow-up analysis because antiarrhythmic pharmacotherapy started after the assessment of TWA and QTD. Follow-up data were available for the remaining 30 patients. $\beta$-Blocker use during the follow-up period was not changed in any patient. TWA and QTD were positive in 24 (80%) and 11 (37%) of these 30 patients, respectively. There were no significant differences between patients with positive and negative TWA results with respect to age, gender, NYHA classification, $\beta$-blocker use, LVEF, LVEDD, maximum QTc interval, and the incidence of a positive QTD result. Although the value for NYHA classification in patients with a positive QTD result was greater than negatives, other clinical variables, including the incidence of a positive TWA result, did not differ for patients with positive and with negative QTD results. During an average follow-up of 13±11 months (range 1 to 35 months), VTs occurred in 13 of 30 patients (43%) including 7 patients who had sustained VTs ($n=5$) and ventricular fibrillation ($n=2$). VTs occurred in 13 of 24 patients (54 %) with a positive TWA result and in none of 6 patients (0%) with a negative TWA result. On the other hand, VTs occurred in 6 of 11 patients (55%) with positive QTD results, and in 7 of 19 patients (37%) with a negative QTD result. Although age, gender, NYHA classification, LVEF, LVEDD, and a positive QTD result did not differ for patients with and without VTs, TWA was significantly related to VT (Table II). In 7 patients with sustained VT or ventricular fibrillation, TWA and QTD were positive in 7 (100%) and 3 patients (43%), respectively. Although no significant difference was shown between TWA and QTD, TWA tends to be related to such life-threatening arrhythmias. Kaplan-Meier event-free curves for TWA and QTD associating defined VT are shown in Figure 1. In Cox regression analysis, TWA was a significant risk stratifier ($P=0.02$), whereas QTD was not. The sensitivity of TWA in predicting VT was 100%, its specificity was 35%, its
positive predictive value was 54%, and its negative predictive value was 100%. In contrast, the sensitivity of QTD in predicting VT was 46%, its specificity was 71%, its positive predictive value was 55%, and its negative predictive value was 63%.

**DISCUSSION**

**Major findings:** To our knowledge, this is the first prospective study to compare the clinical significance of TWA and QTD in the setting of DCM. In this study, TWA was a significant predictor for VT, whereas QTD was not. The two markers were not associated with each other. These results may suggest that temporal
repolarization abnormality is associated more with arrhythmogenesis than with spatial repolarization abnormality in patients with DCM.

TWA and QTD in patients with DCM: The prognosis for patients with DCM has been poor, and half of these deaths occur suddenly and unexpectedly. Previous studies reported that the severity of VT was independently associated with prognosis in patients with DCM. Repolarization inhomogeneities have been closely associated with the pathogenesis of VT. Recent studies have demonstrated that temporal ventricular repolarization inhomogeneity (i.e., TWA) can help to predict an increased risk of VTs in patients with organic heart disease. Although Adachi, et al have reported that the presence of TWA is significantly associated with VT in patients with DCM, no studies have documented this result prospectively. Recently, Klingengeben, et al reported the usefulness of TWA in the setting of congestive heart failure including use of antiarrhythmic drugs. However, antiarrhythmic drugs influence the presence of TWA, as previously reported. In this study, we prospectively assessed the clinical significance of TWA in DCM patients not receiving antiarrhythmic drug therapy. TWA is a significant predictor for VTs. Therefore, TWA may be a useful noninvasive marker for identification of high-risk DCM patients. QTD reflects spatial ventricular repolarization inhomogeneity and has been proposed as a risk marker for VT in patients with coronary artery disease. However, it has had limited success in patients with DCM. Grimm, et al have stated that QTD increased in patients with DCM and VT, but they found its usefulness for arrhythmia-risk prediction limited by the large overlap in QTD for patients with and without VT. Fei, et al have also stated that QTD was not significantly different between patients with and without VT in the setting of DCM. This prospective study supports the previous results because QTD (>65 msec) did not predict VT. In patients with DCM, the myocardium has been damaged diffusely, which may unify the spatial dispersion of repolarization of the myocardium and may decrease the clinical significance of QTD.

Study limitations: The follow-up study population decreased, because of criteria for exclusion from participation in the study and indeterminate test results. Despite this limitation, the study revealed that TWA is a useful marker in patients with DCM. Although only repolarization inhomogeneity markers were analyzed, the mechanism of VT may consist of several factors. Further trials are needed to address this issue.

REFERENCES


