Predicting the Recurrence of Ventricular Tachyarrhythmias from T-Wave Alternans Assessed on Antiarrhythmic Pharmacotherapy: A Prospective Study in Patients with Dilated Cardiomyopathy

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Background: Microvolt T-wave alternans (TWA) has been proposed as a useful index to identify patients at risk of ventricular tachyarrhythmias. Recent studies have demonstrated that antiarrhythmic drugs, such as amiodarone and procainamide, decrease the prevalence of TWA. In this study, we tested whether TWA in patients on antiarrhythmic pharmacotherapy significantly predicts the recurrence of ventricular tachyarrhythmias in patients with dilated cardiomyopathy.

Methods: To evaluate the ability to predict the recurrence of ventricular tachyarrhythmias, determinate TWA and left ventricular ejection fraction (LVEF) were prospectively assessed in 49 patients with ischemic or nonischemic dilated cardiomyopathy on antiarrhythmic pharmacotherapy for sustained ventricular tachycardia (VT) or ventricular fibrillation (VF). The pharmacotherapy consisted of class I (17 patients), III (29 patients), and IV (3 patients) antiarrhythmic drugs. The study endpoint was the first recurrence of sustained VT or VF on treatment during the follow-up period.

Results: TWA was positive on antiarrhythmic pharmacotherapy in 30 patients (61%). During a follow-up of 13 ± 11 months, the sustained VT or VF recurred in 21 of the 41 patients (51%) with available follow-up data. The sensitivity of TWA and LVEF for predicting recurrence of ventricular tachyarrhythmias was 76 and 38%, specificity was 60 and 70%, positive predictive value was 67 and 57%, and negative predictive value was 71 and 52%. Kaplan-Meier event-free analysis revealed that TWA was a significant risk stratifier ($P = 0.02$), whereas LVEF was not.

Conclusions: This prospective study suggests that TWA significantly predicts the recurrence of ventricular tachyarrhythmias, even on antiarrhythmic pharmacotherapy, in patients with dilated cardiomyopathy. TWA may also be a useful marker for evaluating the efficacy of antiarrhythmic drugs for ventricular tachyarrhythmias.

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T-wave alternans; ejection fraction; ventricular tachyarrhythmia; antiarrhythmic drugs; dilated cardiomyopathy

The prevention of serious ventricular tachyarrhythmias responsible for sudden cardiac death

remains a therapeutic target in patients with dilated cardiomyopathy. Microvolt T-wave alternans

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(TWA) has been proposed as a useful noninvasive marker for identifying patients at high risk of ventricular tachyarrhythmias based on organic heart disease.¹⁻⁵ The majority of patients with a history of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) are treated with antiarrhythmic drugs or an implantable cardioverter defibrillator (ICD). Recent studies have demonstrated that antiarrhythmic drugs, such as amiodarone and procainamide, decrease the prevalence of TWA.^{6,7} At present, the usefulness of TWA as a predictor for VT or VF in patients on antiarrhythmic pharmacotherapy is controversial. In the present study, we tested whether TWA measured on antiarrhythmic pharmacotherapy significantly predicts the recurrence of ventricular tachyarrhythmias and whether the predictive value of TWA is better than that of left ventricular ejection fraction (LVEF) measured by echocardiography in patients with ischemic or nonischemic dilated cardiomyopathy.

METHODS

Patient Population

Sixty-four consecutive patients with ischemic or nonischemic dilated cardiomyopathy who underwent empiric antiarrhythmic pharmacotherapy for sustained VT or VF in an intensive care unit or coronary care unit of Toho University Ohashi Hospital between February 1997 and April 2000 enrolled in the study. Patients were excluded from participation if their baseline rhythm was other than normal sinus rhythm, or if they could not undergo exercise testing because of congestive heart failure. Fifteen patients with an indeterminate TWA due to extrasystoles (9 patients), a failure to achieve a heart rate of 105 beats/min (3 patients), or other clinical reasons (3 patients) were also excluded from this study. Therefore, 49 patients were prospectively assessed. All patients gave informed consent prior to enrollment in the study. The characteristics of patients with the determinate test result are shown in Table 1. The study group consisted of 10 women and 39 men with a mean age of 54 ± 14 years, including patients with ischemic (N = 23) and nonischemic (N = 26) cardiomyopathy. The mean New York Heart Association (NYHA) classification at time of noninvasive assessment was 1.6 ± 0.5 . The mean LVEF and left ventricular end-diastolic diameter (LVDD) by echocardiography were $48 \pm 18\%$ and 61 ± 14

Table 1. Patient Demographics and Clinical Characteristics in the T-Wave Alternans Determinate Population

No. of patients	49
Age (years)	54 ± 14
Gender	
Women	10 (20%)
Men	39 (80%)
Dilated cardiomyopathy	
Ischemic	23 (47%)
Nonischemic	26 (53%)
NYHA classification	1.6 ± 0.5
LVEF (%)	48 ± 18
LVDD (mm)	61 ± 14
Antiarrhythmic drugs	
Procainamide (1500–2000 mg/day)	2 (4%)
Disopyramide (300 mg/day)	5 (10%)
Pirmenol (200 mg/day)	1 (2%)
Aprindine (40–60 mg/day)	3 (6%)
Mexiletine (300 mg/day)	4 (8%)
Propafenone (450 mg/day)	1 (2%)
Pilsicainide (150 mg/day)	1 (2%)
Amiodarone (100–400 mg/day)	28 (57%)
Sotalol (160 mg/day)	1 (2%)
Bepidil (200 mg/day)	3 (6%)
Beta-blocker use	17 (35%)
ACE inhibitors use	49 (100%)
ICD implant	12 (24%)

ACE = angiotensin-converting enzyme; ICD = implantable cardioverter defibrillator; LVDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

mm, respectively. Patients were empirically treated with class I (17 patients), III (29 patients), or IV (3 patients) antiarrhythmic drugs as shown in Table 1, soon after admission to our institute. In 17 patients, beta-blockers were used in addition to antiarrhythmic drugs. No patient was taking more than one antiarrhythmic drug, except beta-blockers. Angiotensin-converting enzyme (ACE) inhibitors had been used in all patients. Twelve patients had an ICD implanted during the follow-up period, in addition to receiving antiarrhythmic pharmacotherapy. TWA was not measured during exercise testing prior to starting antiarrhythmic pharmacotherapy because ventricular tachyarrhythmias, including extrasystoles, occurred frequently and were not controlled without antiarrhythmic drugs.

TWA Measurement

Before TWA assessment, class I, III, or IV antiarrhythmic drugs were taken for at least 2, 4, or 2 weeks, respectively. No antiarrhythmic drugs were

withdrawn prior to measuring TWA. The TWA was measured during a supine bicycle exercise test using the CH2000 system (Cambridge Heart Inc., Bedford, MA, USA) during administration of antiarrhythmic drugs, as previously described.^{5,8} Standard ECG leads along with the Frank orthogonal (VM, X, Y, Z) configuration were used. Microvolt-level TWA was measured using the spectral method.⁹ Alternans voltage (Valt) and alternans ratio were computed from the beat domain power spectrum. Valt reflects the characteristic difference in mean T-wave amplitude. Alternans ratio normalizes Valt to background noise and provides a measure of the statistical significance of Valt. The TWA was considered positive when the sustained Valt was $> 1.9 \mu\text{V}$ with an alternans ratio > 3.0 in any orthogonal lead or two consecutive pericordial leads during exercise with a heart rate onset below 70% of predicted heart rate for at least 1 minute. TWA was considered negative when the positive criteria were not met and artifact-free data were available showing a heart rate maintained at a level > 105 beats/minute for at least 1 minute. TWA was defined as indeterminate when the results did not meet either the positive or negative criteria.¹⁰⁻¹² Interpretation of TWA testing was carried out prospectively by investigators blinded to other clinical data.

Echocardiography

Transthoracic echocardiography was performed at the same time as the TWA measurement. LVEF and LVDD were determined by standard techniques.^{13,14} A low LVEF was defined as an LVEF $< 40\%$.

Follow-up and Study Endpoint

All patients were followed as outpatients at our institute, as previously described.⁵ The study endpoint was prospectively defined as the first recurrence of sustained VT or VF determined by standard ECG or 24-hour Holter ECG. Patients in whom antiarrhythmic drugs were changed during the follow-up period because of side-effects or proarrhythmias¹⁵ were excluded from assessment in this prospective study. Nonsustained VT lasting less than 30 sec was not included as a recurrence of ventricular tachyarrhythmia.

Table 2. Comparison between Patients with and without Determinate T-Wave Alternans

	TWA Positive	TWA Negative	P Value
No. of patients	30 (61%)	19 (39%)	
Age (years)	55 ± 14	51 ± 13	NS
NYHA classification	1.7 ± 0.5	1.6 ± 0.5	NS
Beta-blocker use	9 (30%)	8 (42%)	NS
TWA magnitude at eVM (μV)	5.3 ± 2.6	1.1 ± 1.1	< 0.0001
Maximal heart rate with exercise (beats/min)	109 ± 6	105 ± 10	NS
LVEF (%)	44 ± 17	54 ± 16	NS
LVDD (mm)	64 ± 14	56 ± 12	NS

LVDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; TWA = T-wave alternans.

Statistical Analysis

Continuous data were expressed as mean $\pm$ SD and analyzed by Student's *t*-test. Comparisons between clinical variables were evaluated by chi-squared analysis. The association between TWA, LVEF, and the recurrence of ventricular tachyarrhythmias was evaluated by univariate Cox regression analysis. Predictive values of ventricular tachyarrhythmias were also assessed. Time to recurrence of ventricular tachyarrhythmia was estimated by the Kaplan-Meier method, and comparisons between two indices were based on the log-rank test. A value of $P < 0.05$ was considered statistically significant.

RESULTS

T-Wave Alternans

Fifteen patients with an indeterminate test result were excluded from this prospective study. TWA was positive on antiarrhythmic pharmacotherapy in 30 of 49 patients (61%) with a determinate TWA, whereas 19 patients (39%) had negative TWA results. Comparisons of clinical variables between patients with positive and negative TWA tests are shown in Table 2. There was no significant difference between patients with a positive and negative TWA with respect to age, NYHA classification, beta-blocker use, or maximal heart rate with exercise.

Results of Echocardiography

Determination of LVEF and LVDD was performed in all 49 patients with determinate TWA testing. A low LVEF (< 40%) was found in 20 patients (41%). LVEF in patients with positive and negative TWA was $44 \pm 17\%$ and $54 \pm 16\%$, respectively ($P = \text{NS}$), as shown in Table 2. LVDD in patients with positive and negative TWA was 64 ± 14 mm and 56 ± 12 mm, respectively ($P = \text{NS}$).

Arrhythmia-Recurrence and Noninvasive Markers

Eight patients were excluded from the follow-up analysis because of nonarrhythmic cardiac death (2 patients), cessation or change of antiarrhythmic drugs due to proarrhythmia¹⁵ (1 patient) or side-effects (3 patients), or other clinical reasons (2 patients). Follow-up data were available on the remaining 41 patients with determinate TWA test results. TWA was positive in 24 (60%) of these 41 patients. During an average follow-up of 13 ± 11 months (range 1 to 36 months), a recurrence of sustained VT or VF occurred in 16 of 24 patients (67%) with positive TWA, and in 5 of 17 patients (29%) with negative TWA ($P = 0.02$). A recurrence of sustained VT or VF occurred in 8 of 14 (57%) patients with an LVEF < 40%, and in 13 of 27 (48%) patients with an LVEF $\geq 40\%$. The NYHA classification in patients with and without a recurrence of ventricular tachyarrhythmias was 1.5 ± 0.5 and 1.7 ± 0.5 , respectively ($P = \text{NS}$). Although 9 patients with and 11 patients without a recurrence of ventricular tachyarrhythmias were treated with beta-blockers, there was no significant difference between these two groups. There was no significant difference in amiodarone use between patients with and without a recurrence of ventricular tachyarrhythmia.

Predictive Values of TWA and LVEF

The sensitivity of TWA for predicting the recurrence of ventricular tachyarrhythmias was 76%, specificity was 60%, positive predictive value was 67%, and negative predictive value was 71% (Table 3). In contrast, the sensitivity of LVEF for predicting ventricular tachyarrhythmia was 38%, specificity was 70%, positive predictive value was 57%, and negative predictive value was 52%. TWA was a significant univariate predictor ($P = 0.02$), whereas LVEF was not. Kaplan-Meier event-free

Table 3. Predictive Values of T-Wave Alternans and Left Ventricular Ejection Fraction

Test	Sens (%)	Spec (%)	PPV (%)	NPV (%)	P Value
TWA	76	60	67	71	0.02
LVEF	38	70	57	52	NS

LVEF = left ventricular ejection fraction; NPV = negative predictive value; PPV = positive predictive value; Sens = sensitivity; Spec = specificity; TWA = T-wave alternans.

curves for TWA and LVEF are shown in Figure 1. TWA achieved statistical significance by Kaplan-Meier analysis according to the log rank test ($P = 0.02$), but LVEF did not ($P = 0.68$).

DISCUSSION

Major Findings

To our knowledge, this is the first prospective study to test whether TWA measurements made in patients receiving antiarrhythmic pharmacotherapy significantly predict the recurrence of ventricular tachyarrhythmias. In our study, TWA was a significant univariate predictor of the recurrence of ventricular tachyarrhythmias, and Kaplan-Meier event-free analysis showed that TWA is a statistically significant predictor. This prospective study shows that TWA is a useful predictor of the recurrence of ventricular tachyarrhythmias even in patients receiving antiarrhythmic pharmacotherapy. Therefore, antiarrhythmic pharmacotherapy does not compromise the reliability of TWA testing.

TWA and Antiarrhythmic Drugs

Amiodarone and procainamide have been demonstrated to decrease the magnitude of TWA toward the level of negative criteria in patients with ventricular tachyarrhythmias.^{6,7} In our study, TWA was negative in 39% of patients receiving antiarrhythmic pharmacotherapy for sustained VT or VF. Antiarrhythmic drugs appear to decrease the magnitude of TWA in these patients without decreasing the predictive value of TWA. During the follow-up period, the recurrence of VT or VF was suppressed in 71% of patients with a negative TWA test. The decrease seen in TWA in patients on antiarrhythmic drugs may correlate with the suppression of the occurrence of ventricular tachyarrhythmias. On the other hand, TWA was positive in 61% of patients in this study. Antiarrhythmic

Figure 1. Kaplan-Meier event-free curves for ventricular tachyarrhythmias according to T-wave alternans (TWA) (Panel A) and left ventricular ejection fraction (Panel B). TWA-positive patients had more frequent event recurrences ($P = 0.02$).

drugs may not decrease the prevalence of TWA in all patients with a history of ventricular tachyarrhythmias. The discrepancy between our study and previous studies^{6,7} may in part be explained by differences in study protocols, patient selection, and antiarrhythmic drug selection and dose. However, during the follow-up period, VT or VF recurred in 67% of patients with positive TWA, suggesting that a positive TWA test reflects a lack of antiarrhythmic efficacy. The assessment of TWA in patients receiving antiarrhythmic pharmacotherapy may identify patients who would benefit from a change in antiarrhythmic drugs or the use of an ICD.

Although our study and previous studies suggest that antiarrhythmic drugs decrease the prevalence of TWA in some patients with a history of ventricular tachyarrhythmias,^{6,7} the underlying mechanism for this is unclear. The presence of positive TWA is observed in regions of increased dispersion of repolarization.¹⁰ One recent study demonstrated that repolarization alternans at the cellular level accounts for TWA.¹⁶ Antiarrhythmic drugs might reduce these repolarization alternans and decrease TWA amplitude.

Comparison of TWA and LVEF

A previous study reported that LVEF is a powerful predictor of ventricular tachyarrhythmias and that it also was an index of the efficacy of

antiarrhythmic pharmacotherapy to suppress ventricular arrhythmias.¹⁷ In this study, TWA predicted the recurrence and suppression of VT and VF, although LVEF did not. This discrepancy may be explained in part by differences in patient selection. LVEF was relatively better-preserved in the patients in this study than it was in patients enrolled in the previous study, because of the requirement that TWA be assessed during exercise and because of ACE inhibitors use in all patients. Therefore, when LVEF is relatively well-preserved, TWA may be better than LVEF in predicting the recurrence and the suppression of ventricular tachyarrhythmia in patients who are receiving antiarrhythmic drug treatment.

Study Limitations

TWA testing was not assessed prior to starting antiarrhythmic pharmacotherapy in the present study. A more comprehensive evaluation of the effect of antiarrhythmic drugs on TWA testing and on arrhythmia suppression requires that TWA be assessed before and after administration of antiarrhythmic drugs. Nevertheless TWA was able to identify patients at high risk of ventricular tachyarrhythmias despite receiving antiarrhythmic pharmacotherapy. The second limitation was the small sample size of the study population. Despite this limitation, our study revealed the usefulness of TWA in antiarrhythmic pharmacotherapy. How-

ever, we were not able to compare the significance of TWA between the different drug groups because of the small sample size. Further trials involving larger numbers of patients are needed to address this subject.

CONCLUSIONS

This prospective study suggests that TWA significantly predicts the recurrence of ventricular tachyarrhythmias, even in patients receiving antiarrhythmic pharmacotherapy with dilated cardiomyopathy. TWA may also be a useful marker for evaluating the efficacy of antiarrhythmic drugs for ventricular tachyarrhythmias.

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