Usefulness of Microvolt T-Wave Alternans for Prediction of Ventricular Tachyarrhythmic Events in Patients With Dilated Cardiomyopathy: Results From a Prospective Observational Study

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OBJECTIVES
This study was designed to evaluate the ability of microvolt-level T-wave alternans (MTWA) to identify prospectively patients with idiopathic dilated cardiomyopathy (DCM) at risk of ventricular tachyarrhythmic events and to compare its predictive accuracy with that of conventional risk stratifiers.

BACKGROUND
Patients with DCM are at increased risk of sudden death from ventricular tachyarrhythmias. At present, there are no established methods of assessing this risk.

METHODS
A total of 137 patients with DCM underwent risk stratification through assessment of MTWA, left ventricular ejection fraction, baroreflex sensitivity (BRS), heart rate variability, presence of nonsustained ventricular tachycardia (VT), signal-averaged electrocardiogram, and presence of intraventricular conduction defect. The study end point was either sudden death, resuscitated ventricular fibrillation, or documented hemodynamically unstable VT.

RESULTS
During an average follow-up of 14 ± 6 months, MTWA and BRS were significant univariate predictors of ventricular tachyarrhythmic events (p < 0.035 and p < 0.015, respectively). Multivariate Cox regression analysis revealed that only MTWA was a significant predictor.

CONCLUSIONS
Microvolt-level T-wave alternans is a powerful independent predictor of ventricular tachyarrhythmic events in patients with DCM. (J Am Coll Cardiol 2003;41:2220–4) © 2003 by the American College of Cardiology Foundation

Idiopathic dilated cardiomyopathy (DCM) represents the substrate for approximately 10% of sudden cardiac deaths (SCDs) in the adult population (1). Mortality in patients with DCM ranges between 10% and 50% annually, mainly determined by the severity of the disease (2).

Recently, it has been demonstrated that in patients with a history of sustained ventricular tachycardia (VT) or aborted SCD, the implantable defibrillator (ICD) is superior to antiarrhythmic pharmacotherapy in prolonging life (3–5). In these studies, a significant proportion of enrolled patients suffered from DCM. Even in DCM patients without aborted SCD but with syncope as the initial presentation, in whom no arrhythmias could be provoked at electrophysiologic (EP) testing, there was a high incidence of appropriate device therapy (6). However, a recently published study in 104 patients with DCM and a left ventricular ejection fraction (LVEF) ≤0.30 who randomly either did or did not receive the device failed to show benefit from prophylactic ICD therapy (7). This emphasizes the need of better identification of DCM patients at high risk of arrhythmogenic death. Moreover, widespread application of such a risk stratification approach requires noninvasive, inexpensive, and easy-to-perform risk stratification methods.

Analysis of microvolt-level T-wave alternans (MTWA) from the surface electrocardiogram (ECG) has been introduced as a new approach for evaluating arrhythmogenic risk (8–11). Microvolt-level T-wave alternans analysis involves the detection of alterations in T-wave morphology that occur on an every-other-beat basis. Microvolt-level T-wave alternans is thought to reflect the occurrence of localized action potential alternans, which creates dispersion of recovery, which in turn promotes the development of reentrant arrhythmias. In a recent study in patients with heart failure, MTWA was shown to predict the occurrence of arrhythmias (12). However, in that study the majority of patients suffered from coronary artery disease as the underlying structural heart disease. Other investigators have studied the association between MTWA and presence of Holter-documented VT in DCM patients (13), retrospectively analyzed the relationship between MTWA and prior ventricular tachyarrhythmic events in DCM patients (14), and evaluated MTWA as a predictor of ventricular tachy-
arrhythmic events in mixed populations of patients with ischemic and non-ischemic cardiomyopathy (15). Only one other study has evaluated the prognostic value of MTWA in DCM patients (16). Accordingly, this study reports on noninvasive risk stratification in a consecutive series of patients with proven DCM, with particular emphasis on the potential role of MTWA determination.

METHODS

Patient population. Consecutive patients referred to the heart failure clinic of the J. W. Goethe University for diagnosis or for management of heart failure, or to the EP laboratory of the same institution for evaluation of symptomatic arrhythmias, were considered for entry in the present study. Patients were eligible for participation if the following inclusion criteria were met: 1) a confirmed diagnosis of DCM according to accepted criteria (17) (including selective coronary and left ventricular angiography in all patients); 2) no intercurrent illnesses limiting life expectancy; and 3) presence of sinus rhythm at initial presentation. Risk stratification was performed at the first clinical visit/hospitalization when patients were in stable clinical condition. All patients gave informed consent before entering the study.

Follow-up. After discharge, patients were seen in the arrhythmia outpatient clinic at four, eight, and 12 months and at six-month intervals thereafter. Antiarrhythmic medications remained unchanged during follow-up. Information about deceased patients was obtained from family members, their general practitioners, and the hospitals to which they had been admitted. Particular attention was given to the circumstances of each death.

Measurement of MTWA. Microvolt-level T-wave alternans was measured during bicycle exercise, as previously described (10–12). Microvolt-level T-wave alternans was prospectively defined (18) to be positive when sustained alternans were present at the resting heart rate (HR) or had an onset HR ≤110 beats/min. Microvolt-level T-wave alternans was prospectively defined to be negative if the criteria for positivity were not met and at least 1 min of artifact-free data without significant alternans was identified while the HR was maintained at either a level ≤105 beats/min or within 5 beats/min of the maximum HR (as long as the maximum HR was at least 80 beats/min and the patient exercised to maximal effort limited by fatigue or cardiorespiratory symptoms). Microvolt-level T-wave alternans was classified as indeterminate otherwise. Interpretation of MTWA tests was carried out prospectively by a reader (D.M.B.) blinded to clinical data.

Conventional risk stratifiers. Risk assessment included determination of LVEF, HR variability, mean 24-h RR interval, presence of nonsustained VT, baroreflex sensitivity (BRS), and analysis of signal-averaged ECG as previously reported (12). For the tests with continuous variable results, the following cutpoints were prospectively used to define high-risk groups: LVEF ≤35%; mean RR ≤700 ms; for HR variability; standard deviation of normal-to-normal intervals ≤70 ms; and BRS ≤3.0 ms/mm Hg. Intraventricular conduction defect (IVCD) was defined as a QRS duration of ≥120 ms.

Definition of end points. With respect to risk stratification, the following events were prospectively defined as end points of the study: sudden death (19) as death occurring instantaneously within 60 min of a change in symptoms or unexpectedly during sleep; cardiac arrest due to ventricular fibrillation (VF) documented by the emergency service; or hemodynamically unstable VT or VF documented by electrogram storage of an ICD. Heart transplantation was not considered as an end point, but follow-up of patients was censored at the time of this procedure.

Statistics. Kaplan-Meier analysis was used to perform the univariate analyses of the cumulative probability of events in conjunction with the log-rank test. Cox regression analysis was used for the multivariate analysis test using the SAS software package (SAS Institute Inc., Cary, North Carolina). The survival curves in each case were computed starting at the date of risk stratification. Statistical measures of sensitivity, specificity, positive and negative predictive accuracy, relative risk, and their standard deviations were computed from the values and standard errors of survival at the 18-month time point. Data are given as mean ± SD. The hypotheses being tested were single-sided (patients with a positive clinical test result have a higher future event rate than patients with a negative clinical test result), and thus p values reflect single-sided statistical tests. A statistical significance level of p = 0.05 was used. Patients with indeterminate results were not included in the statistical analyses.

RESULTS

Study population and events during follow-up. A total of 137 patients with nonischemic DCM, 31 women and 106 men with a mean age of 55 ± 11 years, were enrolled in the study (Table 1). At study entry, 37 patients (27%) had been fitted with an ICD because of a prior history of cardiac arrest (n = 15), documented sustained VT (n = 12),
syncope (n = 6), or for prophylactic reasons (n = 4). In the remaining 100 patients, there was no prior history of VT/VF or aborted SCD.

In the entire cohort, LVEF averaged 0.29 ± 0.11. Sixty-four percent of patients were treated with digoxin, 91% with angiotensin-converting enzyme inhibitors, 65% with beta-blockers, and 81% with diuretics. The only antiarrhythmic drug used was amiodarone, which was administered to 29 patients (21%).

Patients were followed for up to 18 months (mean 14 ± 6 months). During the follow-up period, one of the specified study end points was observed in 18 patients. Four patients died suddenly, 3 suffered from unstable VT, and 11 were successfully resuscitated from VF. In addition, three patients died from pump failure and two from a noncardiac cause. Six patients underwent heart transplantation.

T-wave alternans. The MTWA outcome was positive in 66 patients (48%), negative in 34 (25%), and indeterminate in 37 (27%). Eighteen of the 37 patients with indeterminate results failed to achieve an HR of 105 beats/min. Of the event patients, 13 were positive, 2 negative, and 3 indeterminate. By Kaplan-Meier analysis, MTWA (p = 0.035) was a statistically significant predictor of events (Fig. 1).

Conventional risk stratifiers. The outcomes of bifurcated conventional risk stratification were as follows (Table 2): LVEF was ≤0.35 in 79%, BRS was ≤3.0 ms/mm Hg in 49%; mean RR was ≤700 ms in 34%; nonspecific ventricular tachycardia (NSVT) was present in 36%; signal-averaged ECG was positive in 24% and indeterminate in 38%; SDNN was ≤70 ms in 38%; and IVCD was present in 48 patients (35%).

Only MTWA and BRS were statistically significant univariate predictors of events in the entire population (Table 2, Fig. 1).

**Table 1.** Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>55 ± 11</td>
</tr>
<tr>
<td>Male gender (% patients)</td>
<td>77</td>
</tr>
<tr>
<td>Medication (% patients)</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>64</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>91</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>65</td>
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<tr>
<td>Diuretics</td>
<td>81</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>21</td>
</tr>
<tr>
<td>Mean follow-up (months)</td>
<td>14 ± 6</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>29 ± 11</td>
</tr>
<tr>
<td>NSVT (%)</td>
<td>36</td>
</tr>
<tr>
<td>BRS (ms/mm Hg)</td>
<td>4.1 ± 4.4</td>
</tr>
<tr>
<td>MTWA (patients/%)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>66 (48%)</td>
</tr>
<tr>
<td>Negative</td>
<td>34 (25%)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>37 (27%)</td>
</tr>
<tr>
<td>IVCD present (% patients)</td>
<td>35</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>90 ± 49</td>
</tr>
<tr>
<td>SAECG + (%)</td>
<td>24</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; BRS = baroreflex sensitivity; IVCD = intraventricular conduction disturbance; LVEF = left ventricular ejection fraction; MTWA = microvolt-level T-wave alternans; NSVT = nonsustained ventricular tachycardia; SAECG = signal-averaged electrocardiogram; SDNN = standard deviation of NN intervals.

Multivariate analysis. The outcomes of the various risk stratification methods were subjected to a Cox regression analysis with the occurrence of end points as the dependent variable. The final model of this analysis included MTWA as the only independent statistical predictor of arrhythmic events (chi-square value 3.87; p = 0.045). We also attempted to adjust for additional covariates of age, gender, and extent of disease as measured by LVEF, but the sample size was too small to allow for this adjustment.

Patients with ICDs. The end point event rate (as determined by Kaplan-Meier analysis) in patients with prior ICDs was 33% at 18 months of follow-up versus 8% in patients without ICDs (p < 0.001). Eleven end point events occurred among the patients with ICDs, and seven among patients without ICDs. In patients with ICDs versus patients without ICDs, the number of patients with a positive MTWA test was 23 (62%) versus 43 (43%) (p < 0.04), the number with a negative MTWA result was 5 (14%) versus 29 (29%) (p < 0.05), and the number with an
indeterminate test result was 9 (24%) versus 28 (28%) (p = NS). The ICD and non-ICD patient subgroups were too small for MTWA to achieve statistical significance within each subgroup. However, the relative risk for MTWA predicting end point events among ICD patients was 2.4 ± 2.2, and for non-ICD patients 1.93 ± 2.2.

DISCUSSION

This prospective study is the first to compare the prognostic value of noninvasive assessment of MTWA to a variety of other currently used risk stratification methods in patients with DCM. The results show that determination of MTWA and BRS are useful in predicting risk for future tachyarrhythmic events in this patient population.

Risk stratification for arrhythmogenic death in DCM.

The prognosis of patients with DCM has been reported to be poor, with mortality rates up to 50% over a two-year follow-up period (2,20). Recent therapeutic advances have improved survival of DCM patients significantly, as indicated by recently published prospective studies (7,21). Nevertheless, sudden arrhythmogenic death is continuing to be one of the leading causes of death in DCM (1).

Depressed left ventricular function appears to be the most powerful risk predictor, but in general it is a better predictor of overall than of arrhythmogenic mortality. At present, there are no reliable strategies to identify DCM patients specifically at high risk for sudden death. For instance, EP testing in DCM has been shown to be of limited value (22,23). Likewise, the presence of NSVT has been evaluated as a marker of arrhythmogenic risk, although the data are mixed (21,24). In a recent prospective study, however, NSVT did not identify DCM patients who would benefit from ICD (21). Few studies have aimed to identify DCM patients at risk for arrhythmogenic death by evaluating autonomic tone (25,26). For example, Yi and colleagues recently showed that reduced HRV is a marker of progressive heart failure (25). However, the prognostic power of autonomic markers for prediction of arrhythmogenic death in DCM remains to be demonstrated. Thus, despite the availability of a very effective therapeutic modality to prevent sudden death—the ICD (3–5)—at present no reliable risk stratification method exists to identify specifically those DCM patients who would benefit from prophylactic device therapy (7).

Repolarization abnormalities to identify DCM patients at risk for tachyarrhythmic events. At a cellular level, myocardium isolated from failing animal and human hearts reveals significant EP abnormalities, including repolarization (27). There is experimental evidence that alteration of repolarizing K + channel expression in failing myocardium predisposes to those repolarization abnormalities that may give rise to malignant reentry arrhythmias (27). Accordingly, it has been proposed to evaluate the prognostic yield of new ECG measures of repolarization, such as QT interval dispersion (27) or MTWA (10–12,16). Concerning the first method, some investigators found prognostic information of prolonged QT dispersion in CHF (27), others did not (28).

Microvolt-level T-wave alternans is a new promising noninvasive method of evaluating repolarization abnormalities. Experimental and clinical observations indicate that MTWA can be associated with an increased propensity for serious ventricular arrhythmias. The precise EP basis for MTWA remains to be elucidated; at present, the most likely hypothesis is that alterations in action potential duration occurring discordantly in the myocardium causes a greater QT dispersion, which leads to wavefront fractionation and reentry. Evidence for this mechanism as the major predictor for MTWA has recently been provided by experiments applying the technique of high-density optical mapping with voltage-sensitive dyes to a guinea pig Langendorff preparation (29). Repolarization phases of the action potentials exhibited significant alternans-type beat-to-beat oscillations corresponding to ECG–observed MTWA. As to the ionic mechanisms underlying MTWA, it has been recently shown that beat-to-beat changes in intracellular Ca 2+ modulate the repolarizing currents in the heart, thus contributing to MTWA (30).

The results of the present study demonstrate that MTWA-positive patients are at particularly high risk for tachyarrhythmic events. Perhaps equally important is the finding that only occasional patients with a negative MTWA test suffered from a sustained VT or sudden death. Before the present study, only one smaller series has recently been published that examined the prognostic value of
MTWA in DCM. Kitamura et al. followed these patients over a mean of 21 months, during which 12 arrhythmic events occurred (16). Similar to our study, these authors found that MTWA was a powerful risk stratifier in this patient population. Clearly, these findings as well as ours need to be confirmed in future interventional trials evaluating the benefit of prophylactic ICD implantation.

**Study limitations.** In the present study, 27% of patients were enrolled after having received an ICD. These patients had themselves already declared as being at high risk. However, we decided to include them in our study to enrich the number of predefined study end points in order to facilitate evaluation of MTWA as a new risk stratification method. Moreover, only hemodynamically unstable ventricular tachyarrhythmic events were counted as end points in these ICD recipients. In this study, 27% of patients had an indeterminate MTWA result, 49% of whom failed to achieve an HR of 105 beats/min during exercise. Improvements in the exercise protocol and in MTWA analysis technology are expected to reduce this rate in the future.

**Conclusions.** The findings of this prospective study indicate that noninvasive determination of MTWA, particularly when assessed together with autonomic markers such as BRS, holds promise in identifying DCM patients at high risk of future ventricular tachyarrhythmic events.

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**REFERENCES**