Role of Microvolt T-Wave Alternans in Assessment of Arrhythmia Vulnerability Among Patients With Heart Failure and Systolic Dysfunction
Primary Results From the T-Wave Alternans Sudden Cardiac Death in Heart Failure Trial Substudy

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Background—Sudden cardiac death remains a leading cause of mortality despite advances in medical treatment for the prevention of ischemic heart disease and heart failure. Recent studies showed a benefit of implantable cardioverter defibrillator implantation, but appropriate shocks for ventricular tachyarrhythmias were noted only in a minority of patients during 4 to 5 years of follow-up. Accordingly, better risk stratification is needed to optimize patient selection. In this regard, microvolt T-wave alternans (TWA) has emerged as a potentially useful measure of arrhythmia vulnerability, but it has not been evaluated previously in a prospective, randomized trial of implantable cardioverter defibrillator therapy.

Methods and Results—This investigation was a prospective substudy of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) that included 490 patients at 37 clinical sites. TWA tests were classified by blinded readers as positive (37%), negative (22%), or indeterminate (41%) by standard criteria. The composite primary end point was the first occurrence of any of the following events: sudden cardiac death, sustained ventricular tachycardia/fibrillation, or appropriate implantable cardioverter defibrillator discharge. During a median follow-up of 30 months, no significant differences in event rates were found between TWA-positive or -negative patients (hazard ratio 1.24, 95% confidence interval 0.60 to 2.59, \(P = 0.56\)) or TWA-negative and nonnegative (positive and indeterminate) subjects (hazard ratio 1.28, 95% confidence interval 0.65 to 2.53, \(P = 0.46\)). Similar results were obtained with the inclusion or exclusion of patients randomized to amiodarone in the analyses.

Conclusions—TWA testing did not predict arrhythmic events or mortality in SCD-HeFT, although a small reduction in events (20% to 25%) among TWA-negative patients cannot be excluded given the sample size of this study. Accordingly, these results suggest that TWA is not useful as an aid in clinical decision making on implantable cardioverter defibrillator therapy among patients with heart failure and left ventricular systolic dysfunction. (Circulation. 2008;118:2022-2028.)

Key Words: defibrillation ■ electrocardiography ■ heart failure

Sudden cardiac death remains a leading cause of mortality despite advances in medical treatment for the prevention of ischemic heart disease and heart failure. Recent studies of the implantable cardioverter defibrillator (ICD) showed significant reductions in all-cause and sudden death mortality in certain high-risk cohorts of patients.\(^1\)\(^-\)\(^8\) Two studies in particular are most responsible for the dramatic increase in ICD use for primary prevention. Specifically, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) evaluated patients with symptomatic heart failure (New York Heart Association class II to III) and left ventricular systolic dysfunction,\(^6\) whereas the second Multicenter Automatic Defibrillator Implantation Trial (MADIT II) evaluated patients with coronary artery disease and ischemic cardiomyopathy.\(^5\) Both studies showed a benefit of ICD implantation, but appropriate shocks for ventricular tachyarrhythmias were only noted in a minor-
Microvolt T-wave alternans (TWA) is a noninvasive test of arrhythmia vulnerability. The results of previous observational studies showed that TWA predicts ICD shocks or arrhythmic events in diverse patient populations, including those with heart failure and ischemic cardiomyopathy. This led to the hypothesis that TWA could be used to identify patients most likely to benefit from ICD implantation; however, the value of TWA for risk stratification has not been evaluated previously in a large, randomized trial of ICD therapy. Accordingly, the present study was designed to test prospectively the hypothesis that TWA is a clinically important risk stratifier in a subgroup of the SCD-HeFT cohort.

Methods

This investigation was a prospective substudy of the SCD-HeFT trial. In SCD-HeFT, 2521 subjects were randomized in equal proportions to receive ICD therapy, amiodarone, or placebo. In the TWA substudy, 490 SCD-HeFT patients were enrolled at 37 clinical sites. All patients gave written informed consent, and the present study was approved by the institutional review board at each participating site. In addition to the inclusion/exclusion criteria for the main trial, the only other inclusion criteria were the presence of sinus rhythm on the day of evaluation and the ability to walk on a treadmill. Clinical sites that participated in the substudy were encouraged to enroll all patients who were enrolled in the main study at that site, with the exception of those with absolute contraindications as noted above. This approach was intended to simulate clinical practice and provide the most accurate assessment of the utility of TWA in this population, to avoid the potential selection bias of excluding patients because of ambient ventricular arrhythmias (ie, frequent premature ventricular contractions), deconditioning, or heart failure status.

TWA testing was conducted with submaximal treadmill exercise to achieve a heart rate of 120 bpm for at least 2 minutes. Beta-adrenergic blockers were withheld for at least 24 hours before the study, because these agents suppress TWA and increase the number of determinate TWA tests due to chronotropic incompetence. Careful skin preparation that included mild abrasion was performed to reduce the skin-electrode impedance. Special high-resolution electrodes (High-Res, Cambridge Heart Inc, Bedford, Mass) were used to minimize noise. ECG leads were placed at the standard precordial lead positions (V1 through V6) and in an orthogonal X, Y, Z configuration, as described previously. TWA was measured with the CH2000 system (Cambridge Heart Inc) with a spectral method of analysis (D10 algorithm) designed to allow detection of alternans in the microvolt range of amplitude.

TWA was prospectively defined as positive when it was sustained for at least 1 minute with an onset heart rate ≤110 bpm, alternans amplitude ≥1.9 μV, and alternans ratio (signal-to-noise ratio) ≥3 in the vector magnitude lead, any orthogonal lead, or 2 consecutive precordial leads (TWA+). TWA was defined as negative if the criteria for a positive test were not met, if no significant alternans was seen for 1 minute while the heart rate was ≥105 bpm, and if the tracing was not obscured by noise and had <10% ectopic beats (TWA−). Otherwise, TWA was considered indeterminate.

When an indeterminate test was obtained, investigators were instructed to repeat the test the same day when possible. Data were analyzed by 2 experienced readers who were blinded with respect to the clinical data and randomization status of the patient. The arrhythmic or mortality risk of patients with indeterminate TWA results is reported to be similar to that of TWA-positive patients, and these groups are often combined for analysis. Therefore, comparisons of TWA-negative (positive or indeterminate TWA) with TWA-positive patients were also performed.

Patients were followed up clinically as part of SCD-HeFT every 3 months. The composite primary end point for the present substudy was the first occurrence of any of the following events: sudden cardiac death, sustained ventricular tachycardia/fibrillation, or appropriate ICD discharge. Sudden cardiac death was defined as death within 1 hour of the onset of symptoms or during sleep without any other identified cause. An appropriate ICD discharge was a shock delivered for a persistent ventricular tachyarrhythmia. Of note, ICD pulse generators were uniformly programmed for a single zone (rate cutoff 188 bpm or 320 ms) with prolonged detection (18/24 intervals) to reduce the incidence of shocks for self-terminating arrhythmias. The primary hypothesis was that patients who were TWA+ were more likely to experience a primary end-point event than those who were TWA−. The secondary hypothesis was that patients who were TWA+ and received an ICD were more likely to have appropriate ICD discharges than those who were TWA− and received an ICD. All end points, including the classification of death and ICD discharges, were adjudicated by event committees blinded to the results of TWA testing. Moreover, the interpretation of the results of TWA testing was completed and the database closed while the primary randomization of the main trial was still intact and before any end-point analyses were performed. For this reason, it was unknown at the time of enrollment whether patients randomized to drug therapy were receiving amiodarone or placebo. Because amiodarone is reported to decrease TWA amplitude, subjects taking this medication were initially excluded from the primary end-point analyses prospectively. For completeness, however, results are also provided for the entire substudy population, including those randomized to amiodarone.

The sample size required for the present study was calculated as follows. Of the enrolled patients, it was assumed that 45% of studies would be TWA+ and that TWA would have a sensitivity of 70% for sudden death or tachyarrhythmic events (ie, of the patients who experienced an event, 70% would be TWA+). The annual rate of sudden cardiac death was assumed to be 5%, all patients would be followed up for a minimum of 2.5 years after enrollment, and the tachyarrhythmic event rate for triggering a defibrillator discharge in the ICD arm would be twice the underlying sudden death rate. The combination of all of these assumptions resulted in the projection of a 3-fold increased number of events over 2.5 years in the TWA+ group compared with the TWA− group (29% versus 10%). Given these assumptions, 138 patients with interpretable studies from the ICD and placebo arms combined were required to provide 90% power for detecting a difference of this magnitude for the primary hypothesis. With the assumption that 20% of patients would have studies with indeterminate results and with an allowance for a 5% rate of withdrawals or loss to follow-up, the total sample size required was 175 patients.

All data are presented as mean±SD, except where noted. Continuous variables were compared with t tests or ANOVA, and discrete variables were compared with the conventional χ² test or Fisher exact test. Event-free survival was calculated by the Kaplan–Meier method. The significance of differences in event-free survival between groups was assessed with a stratified Cox proportional hazards regression model, with the analysis stratified on the basis of the patient’s randomized treatment assignment in the main trial. Relative risks were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs) and were calculated with the Cox model. A P value <0.05 was considered statistically significant.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.
The patient population evaluated was typical of those with mild to moderate heart failure, and they were very similar to the overall SCD-HeFT population. Specifically, the cohort in the present substudy (n=490) was 76% men, with a mean age of 59±12 years and left ventricular ejection fraction of 24±7%. Ischemic heart disease was present in 49% of subjects, and 71% had New York Heart Association class II heart failure functional status at the time of enrollment. The baseline QRS duration was 115.6±30.9 ms, and 31% of subjects had QRS prolongation (>120 ms). This cohort was well-treated medically, with 96% receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and 74% receiving β-adrenergic blockers before TWA testing. Diuretics were used by 83% of subjects, and 64% were receiving digoxin. Of note, none of these characteristics differed from the larger population randomized in SCD-HeFT. The patients enrolled in the present substudy represented 45±22% of all patients enrolled in the main study at these 37 clinical sites. One-hundred-forty-six patients were randomized to amiodarone therapy, 178 to placebo therapy, and the remaining 166 to ICD implantation. No statistically significant differences were found in any clinical characteristics among the therapy assignments.

TWA results were classified as positive in 37% of subjects, negative in 22%, and indeterminate in 41%. The indeterminate rate was higher than expected but was independent of randomization assignment. Specifically, 38% of placebo patients, 40% of ICD patients, and 45% of amiodarone patients had indeterminate TWA results (P=0.36). Similarly, the frequencies of TWA-positive or -negative results were also independent of randomization assignment. During a median follow-up period of 30 months, the primary end point was observed in 75 subjects, including 27 subjects with sudden death, 3 with resuscitated cardiac arrest, 40 with sustained ventricular tachycardia, and 25 with appropriate ICD discharge. Of note, patients could experience more than 1 tachyarrhythmia event (eg, ventricular tachycardia leading to ICD discharge), but they reached the primary end point with the first such episode. During the follow-up period, 81 subjects died of any cause. The distribution of deaths and events comprising the composite end point grouped by TWA classification is shown in the Table.

As noted above, the drug randomization of patients was unknown at the time of enrollment. Patients randomized to amiodarone therapy (n=146) were excluded from the initial analysis prospectively. Accordingly, the prespecified primary analysis was restricted to patients randomized to placebo or ICD therapy. These results are shown in Figure 1A; no significant difference in event-free survival was found between TWA-positive and -negative patients (HR 1.24, 95% CI 0.60 to 2.59, P=0.56). Similarly, event-free survival did not differ between TWA-negative and TWA-nonnegative (positive or indeterminate) subjects (HR 1.28, 95% CI 0.65 to 2.53, P=0.46; Figure 1B). It is noteworthy that the curves were largely overlapping for at least 1 year, with TWA-negative patients having an event rate of 10.2% at 12 months (ie, 89.8% event-free survival).

Several preplanned secondary analyses were performed, including an evaluation of TWA to predict the composite end point of appropriate ICD discharge or sudden death in the ICD cohort. Kaplan–Meier analysis showed no significant differences between TWA-negative and -nonnegative groups (P=0.64). The event rates at 36 months were 21.7% for TWA-negative subjects and 25.2% for TWA-nonnegative subjects. Analyses of all-cause mortality based on TWA results in the placebo, ICD, or combined groups also showed no statistically significant differences for any comparisons. Subjects randomized to amiodarone therapy were excluded from the primary analyses; however, as noted above, the TWA results of these subjects did not differ from those in the placebo or ICD arms of SCD-HeFT. Accordingly, further analyses were performed that included the amiodarone group. Results comparing TWA-negative and -nonnegative subjects for the entire cohort (490 patients) are presented in Figure 2. Again, no statistical difference in event-free survival was found between groups (HR 1.11, 95% CI 0.63 to 1.95, P=0.72). The event rate at 36 months for the TWA-negative group was 14.9%, whereas the event rate for the TWA-nonnegative group was 16.5%. Analysis of TWA-positive and -negative patients, excluding the indeterminate subjects, also showed no significant difference (HR 1.17, 95% CI 0.63 to 2.18, P=0.61).

Previous studies reported that TWA is less predictive of arrhythmic events in the presence of QRS prolongation or bundle-branch block.29,30 Accordingly, the primary and secondary end points were analyzed with subjects with QRS prolongation (≥120 ms) excluded. These retrospective analyses again showed no significant predictive value of TWA among subjects with narrow QRS duration. Finally, analyses were performed to assess the predictive value of TWA separately among patients with ischemic and nonischemic causes of left ventricular systolic dysfunction. Again, no
significant predictive values of TWA were found among subjects with either cause of heart failure. In the ischemic subgroup (n=240), the HR was 0.72 (P=0.41, 95% CI 0.34 to 1.55) for the comparison of TWA-negative and -nonnegative subjects, whereas in the nonischemic subgroup (n=250), the HR was 1.67 (P=0.21, 95% CI 0.71 to 3.99).

Discussion
The present study was the first prospective evaluation of TWA to predict arrhythmia vulnerability in a randomized trial for ICD therapy for prevention of all-cause mortality. The primary results of this study showed that TWA was not a useful test to predict arrhythmic events in SCD-HeFT. Specifically, TWA results did not predict life-threatening ventricular arrhythmias, appropriate shocks, or all-cause mortality in the present cohort.

Multiple previous studies of different cohorts showed a better predictive value of TWA for arrhythmic events. Several explanations are possible for these discrepant findings. Several previous studies enrolled some low-risk patients, such as those undergoing evaluation of supraventricular arrhythmias or those with coronary artery disease and a preserved left ventricular ejection fraction. Such patients have a low risk of arrhythmic events or abnormal TWA results, so this will tend to overestimate the negative predictive value of the test. Other single-center studies are subject to selection bias if consecutive patients are not enrolled. In addition, the uncontrolled use of ICD therapy may bias results, because ICD shocks are a major component of end-point events. In the present study, sites were encouraged to enroll all patients in sinus rhythm who could walk on a treadmill, and ICD implantation was determined randomly to minimize selection bias. In addition, uniform programming of devices was maintained, with a high heart rate cutoff, (188 bpm), long detection intervals, and shock therapy only to minimize therapy for self-terminating events. Interestingly, a recent large study also showed a disappointing negative
predictive value for TWA among high-risk patients with left ventricular systolic dysfunction.\textsuperscript{31}

The rate of indeterminate findings was higher than reported with previous studies of TWA. This occurred despite on-site training of each center with technical support during the initial studies, as well as a recommendation to repeat indeterminate tests the same day when possible. Moreover, fewer than 10% of indeterminate results were due to technical problems, such as noise or protocol violations. Rather, frequent ectopy or an inadequate heart rate response was the primary reason for the indeterminate studies. The cause of this high indeterminate rate is unclear. The number of centers in the present study was much larger than previous studies that were conducted at 1 or only several highly experienced sites.\textsuperscript{12,13,15–23} Moreover, sites were encouraged to enroll all patients, even if frequent ectopy or deconditioning was present that would increase the likelihood of an indeterminate study, whereas many previous studies excluded such patients by design to reduce the indeterminate rate. As such, we feel that the present results are more representative of the application of this technology to the general heart failure population and to physicians using this test for risk stratification.

In the present study, TWA measurements were performed after \(\beta\)-blockers had been withheld for 24 to 36 hours. This strategy is used because full \(\beta\)-blockade markedly reduces TWA magnitude, out of proportion to the effect of these drugs on mortality or ICD shocks, and increases the number of indeterminate tests due to a blunted heart rate response with exercise.\textsuperscript{25} Of note, other drugs with no impact on mortality, such as amiodarone and procainamide,\textsuperscript{7,32} also decrease TWA magnitude and prevalence, which suggests that they also would reduce the prognostic value of TWA. For these reasons, \(\beta\)-blockers and antiarrhythmic drugs are often\textsuperscript{13,19–23,31} but not always\textsuperscript{15–18} withheld when TWA is measured. A study comparing the predictive value of TWA in patients with and without \(\beta\)-blocker use has not been performed.

The present study should be interpreted in light of certain methodological limitations. The number of patients studied was relatively small, so we cannot rule out that the HRs observed would truly represent a 20% to 25% reduction of arrhythmic events among TWA-negative patients; however, the number of patients studied was larger and the duration of follow-up was longer than in most previous studies of TWA. Moreover, the 10.2% primary event rate at 1 year among TWA-negative subjects makes it very unlikely that TWA testing would be useful to stratify patients for ICD implantation. The present substudy included 19% of the entire SCD-HeFT population, so we cannot exclude that different results would have been observed in other patients in the main study; however, 37 clinical sites participated in the present substudy, and patient characteristics were very similar to the main study. Consequently, it is very likely that these were representative patients and results. Another potential limitation is that the present study was performed on a very restricted group of patients with systolic dysfunction and New York Heart Association II or III heart failure symptoms. Accordingly, we cannot extrapolate these results to other groups of patients, such as those with more preserved ejection fractions or without symptomatic heart failure. Finally, TWA studies were performed after \(\beta\)-blockers had been withheld for 24 to 36 hours, as noted above. Although this strategy is commonly used in clinical studies of TWA, it is unknown whether the predictive accuracy of this test is affected by a transient reduction in \(\beta\)-blockade.

In summary, in a cohort of 490 subjects enrolled in SCD-HeFT, TWA testing did not predict arrhythmic events or mortality. Accordingly, these results suggest that TWA should not be used to make clinical decisions about ICD therapy among patients who meet SCD-HeFT criteria for implantation (ie, symptomatic heart failure and left ventricular systolic dysfunction). Further prospective studies of TWA, particularly with prespecified or randomized allocation of ICD therapy,\textsuperscript{33} are needed to better define the role of this test for risk stratification of sudden death.
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Dr Gold has received a research grant from Cambridge Heart and serves as a consultant/advisory board member for Medtronic, Boston Scientific, and St Jude Medical. Dr Costantini serves as a consultant/advisory board member for Boston Scientific and St Jude Medical. Dr Poole has received research grants from HAT (National Institutes of Health) and Biotronik (REPLACE Study) and serves on the speakers’ bureaus of Boston Scientific, Sorin, Medtronic, and Biotronik. Dr Mark has received a research grant from Medtronic and serves as a consultant/advisory board member for Medtronic. Dr Lee has received a research grant from Cambridge Heart and has ownership interest in Cameron Health; serves as a consultant/advisory board member for Philips and Boston Scientific; and is the founder and an employee of the Seattle Institute for Cardiac Research.

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Clinical Perspective

Sudden cardiac death remains a leading cause of mortality despite advances in medical treatment for the prevention of ischemic heart disease and heart failure. Studies of the implantable cardioverter defibrillator (ICD) showed significant reductions in mortality among certain high-risk cohorts of patients. Recently, there has been a dramatic increase in ICD use for primary prevention, largely because of the results of 2 studies: the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) and the second Multicenter Automatic Defibrillator Implantation Trial (MADIT II). However, both studies showed that shocks for ventricular tachyarrhythmias occurred in only 25% to 35% of subjects during 4 to 5 years of follow-up. This suggests that many ICD patients may not benefit from this invasive therapy and that better risk stratification is needed to optimize patient selection. In this regard, microvolt T-wave alternans (TWA) is a noninvasive test of arrhythmia vulnerability. Previous observational studies showed that TWA predicted ICD shocks or arrhythmic events in diverse patient populations. This has led some to propose using TWA to identify patients most likely to benefit from ICD implantation; however, the value of TWA for risk stratification had not been evaluated previously in a randomized trial of ICD therapy. In the present study, 490 patients enrolled in SCD-HeFT underwent TWA testing and were followed up prospectively. TWA testing did not predict arrhythmic events or mortality in the cohort as a whole or in subgroups with ischemic or nonischemic cardiomyopathy. Accordingly, these results suggest that TWA is not useful as an aid in clinical decision making about ICD therapy among patients with heart failure and left ventricular dysfunction.

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