“Indeterminate” Microvolt T-Wave Alternans Tests Predict High Risk of Death or Sustained Ventricular Arrhythmias in Patients With Left Ventricular Dysfunction

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OBJECTIVES
This study tested the hypothesis that an “indeterminate” microvolt T-wave alternans (MTWA) test, when due to ectopy, unsustained MTWA, or low exercise heart rate (HR), has prognostic significance similar to a positive MTWA test.

BACKGROUND
MTWA testing, used to stratify risk of sudden or total mortality in patients with structural heart disease, has been limited by a substantial number of “indeterminate” tests. Indeterminate tests are due to patient factors—excessive ventricular ectopy during exercise, unsustained MTWA, or failure to achieve a HR of 105 beats/min for 1 min—or technical factors such as a noisy recording or an exercise protocol that causes an excessively rapid rise in HR.

METHODS
Patients in sinus rhythm with left ventricular ejection fraction ≤0.40 underwent MTWA exercise tests, analyzed with the spectral method and classified by a computerized interpretation algorithm. The primary end point was all-cause mortality or documented non-fatal sustained ventricular arrhythmia (SVA). “Indeterminate” tests were reviewed jointly by 2 readers blinded to subsequent events to determine the primary reason for indeterminacy.

RESULTS
Indeterminate MTWA tests may be due to patient factors—excessive ventricular ectopy during exercise, unsustained MTWA, or low exercise HR—or technical factors such as a noisy electrocardiogram, unsustained MTWA, or failure to achieve a HR of 105 beats/min for 1 min—or technical factors such as a noisy recording or an exercise protocol that causes an excessively rapid rise in HR.

CONCLUSIONS
In patients with left ventricular dysfunction, an “indeterminate” MTWA test due to patient factors predicted death or SVA at least as well as a positive test. (J Am Coll Cardiol 2006; 48:1399–404) © 2006 by the American College of Cardiology Foundation
from study to study but also have substantially different mortality rates. We hypothesized that an indeterminate MTWA test due to the patient factors would have similar prognostic significance to a positive MTWA result. Further, we predicted that indeterminate MTWA due to technical factors would not pose a substantial risk.

METHODS

Patient selection. The T-Wave Alternans in Congestive Heart Failure Study was conducted at 11 clinical centers in the U.S. and has been described previously (5,7). The institutional review board at each clinical center approved the protocol, and written, informed consent was obtained from all patients before their enrollment. Patients were eligible if they were 18 years or older, had left ventricular ejection fraction (LVEF) ≥0.40, stable sinus rhythm, and were able to exercise on a treadmill or bicycle. Exclusions included unstable angina, class IV heart failure, atrial fibrillation, or prior sustained ventricular arrhythmia (SVA). The current analysis was prespecified in the original National Institutes of Health grant proposal.

Follow-up. Follow-up was conducted 1 month after the MTWA test and every 4 months thereafter. During follow-up visits, data were collected on patients’ interim medical and cardiovascular drug histories.

MTWA testing. Patients underwent MTWA testing during light bicycle or treadmill exercise while receiving their usual medications, including beta blocker therapy. Careful skin preparation and high-resolution electrodes (High-Res, Cambridge Heart, Inc., Bedford, Massachusetts) were used to reduce noise. The MTWA tests were performed during a heart rate (HR)-based exercise protocol and recorded on CH2000 or Heartwave Systems (Cambridge Heart, Inc.). Results were classified as positive, negative, or indeterminate by a computerized interpretation algorithm (Version D10, Cambridge Heart, Inc.).

The MTWA tests were classified as positive if there was ≥1 min of MTWA with an onset at a HR ≤110 beats/min that sustained as long as HR remained above the patient-specific onset HR. A test was classified negative if sustained MTWA was not present at an onset HR ≤110 beats/min and if there was ≥1 min at HR ≥105 beats/min in sinus rhythm with noise level <2 μV and ectopy <10%. Otherwise, a test was classified as indeterminate (8). On the basis of these definitions, an indeterminate MTWA test may be caused by patient factors or technical factors. Patient factors include: 1) failure to maintain HR between 105 and 110 beats/min for ≥1 min, 2) unsustained MTWA, or 3) excessive ectopy during exercise. Technical factors include: 1) a noisy recording, or 2) a rapid rise in HR through the target exercise HR range of 105 to 110 beats/min (8). The number of technically indeterminate tests can be reduced by immediately repeating the test (12,16).

Tests that were classified as “indeterminate” by the computerized algorithm were subsequently reviewed jointly by 2 expert readers blinded to patients’ history and subsequent clinical events to determine the primary reason for indeterminate MTWA tests. They discussed each indeterminate case to reach a consensus.

End points. As specified in the protocol (7), end points were adjudicated by an independent, external events committee that was unaware of the MTWA test results and that used the modified Hinkle-Thaler classification (17) for cause of death used in MUSST (Multicenter Unsustained Tachycardia Trial) (18). The events committee reviewed the primary end point case report forms and source documents, which included a narrative of the event and other pertinent data. The primary end point used in this study included all-cause mortality and documented non-fatal SVA (including ICD shocks with intracardiac electrograms documenting rapid ventricular tachycardia or ventricular fibrillation).

Statistical analysis. Follow-up data were censored on the date of heart transplantation or last follow-up. The time course of the primary end point, stratified by MTWA result, was estimated by the Kaplan-Meier method. The association between MTWA and primary end point was assessed with Kaplan-Meier product-limit estimates of the survival functions and tested with a log-rank test (19). The 24-month event rate, estimated by the Kaplan-Meier method, was used to describe the outcome of patients classified by MTWA, and Cox proportional hazards regression was used to estimate the hazard ratio and 95% confidence intervals (CIs) (20).

RESULTS

The baseline characteristics of the 549 participants, broken down by MTWA test result, are listed in Table 1. Overall, their mean age was 56 ± 13 years; 71% were men, 49% had ischemic cardiomyopathy, and 51% had nonischemic cardiomyopathy. Two-thirds of the participants were in New York Heart Association functional class II or III, and the mean ejection fraction was 0.25. About 80% of the participants were receiving beta blockers. The p values in Table 1 refer to the comparison of patients with positive versus indeterminate MTWA results. Compared with patients with positive MTWA results, patients with indeterminate results were older, had higher LVEF, and were more likely to have ischemic cardiomyopathy and a prolonged QRS.
duration. Fewer had a history of hospital stays for congestive heart failure or treatment with digoxin.

During the review of 198 MTWA tests classified as “indeterminate” by the automated reader (7), data from a repeat test were found for 7 participants. On the basis of the automated reading of this second test, 7 participants were reclassified—6 as “negative” and 1 as “positive”—leaving 191 participants in the indeterminate category. Of the 191 participants with an indeterminate result, there was insufficient information to determine the cause of indeterminacy in 4 cases. Consequently, all analyses of causes of indeterminacy were performed on the remaining 187 participants.

There were 51 primary outcome events (40 deaths and 11 non-fatal SVA) during 2 years of follow-up (mean follow-up 20 ± 6 months). The 2-year product-limit event rates for the primary end point, all-cause mortality or non-fatal SVA, in participants with negative, positive, or indeterminate MTWA tests, were 2.4%, 12.3%, and 17.8%, respectively (Fig. 1). Figure 2 illustrates the distribution of

Table 1. Baseline Characteristics for Patients With Negative, Positive, and Indeterminate Microvolt T-Wave Alternans (n = 549)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Negative (n = 195)</th>
<th>Positive (n = 163)</th>
<th>Indeterminate (n = 191)</th>
<th>p Value*</th>
</tr>
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<tbody>
<tr>
<td>Age, yrs</td>
<td>53 ± 13</td>
<td>55 ± 12</td>
<td>60 ± 12</td>
<td>&lt;0.001</td>
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<tr>
<td>Male</td>
<td>63</td>
<td>79</td>
<td>73</td>
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<tr>
<td>White race</td>
<td>54</td>
<td>45</td>
<td>58</td>
<td>0.02</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>50</td>
<td>40</td>
<td>54</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>45</td>
<td>59</td>
<td>58</td>
<td>0.90</td>
</tr>
<tr>
<td>Current smoker</td>
<td>14</td>
<td>14</td>
<td>8</td>
<td>0.08</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>29</td>
<td>28</td>
<td>32</td>
<td>0.35</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>45</td>
<td>41</td>
<td>47</td>
<td>0.23</td>
</tr>
<tr>
<td>CABG surgery before enrollment</td>
<td>25</td>
<td>23</td>
<td>34</td>
<td>0.35</td>
</tr>
<tr>
<td>Previous admission for CHF</td>
<td>53</td>
<td>68</td>
<td>53</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>New York Heart Association CHF class</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No prior CHF or class I</td>
<td>37</td>
<td>33</td>
<td>35</td>
<td>0.47</td>
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<tr>
<td>Class II</td>
<td>45</td>
<td>45</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>18</td>
<td>22</td>
<td>26</td>
<td></td>
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<tr>
<td>LVEF</td>
<td>0.26 ± 0.09</td>
<td>0.23 ± 0.08</td>
<td>0.27 ± 0.08</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>QRS duration &gt; 120 ms</td>
<td>21</td>
<td>26</td>
<td>37</td>
<td>&lt;0.05</td>
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<tr>
<td>Drugs at enrollment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>88</td>
<td>80</td>
<td>76</td>
<td>0.34</td>
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<td>ACE inhibitor/ARB</td>
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<td>86</td>
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<tr>
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<tr>
<td>Anti-lipid</td>
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<td>42</td>
<td>49</td>
<td>0.23</td>
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Age and left ventricular ejection fraction (LVEF) are mean ± SD. All other values are %. *p values refer to positive versus indeterminate microvolt T-wave alternans test.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft; CHF = congestive heart failure.

Figure 1. Kaplan-Meier estimates of death or non-fatal sustained ventricular arrhythmia comparing patients with negative, positive, and indeterminate microvolt T-wave alternans (MTWA) results. The 2-year event rates were (bottom to top): negative 2.4%, positive 12.3%, and indeterminate 17.8%. There was no significant difference between the positive and indeterminate curves (log-rank test).

Figure 2. Causes of indeterminate microvolt T-wave alternans (MTWA) tests. Only 6.4% of the indeterminate MTWA results were due to technical factors; the remainder were due to patient factors. BPM = beats/min; HR = heart rate.
Indeterminate T-Wave Alternans Test

Figure 3. Kaplan-Meier estimates of death or non-fatal sustained ventricular arrhythmia at 2 years of follow-up, comparing subgroups of patients with indeterminate MTWA results and those with positive MTWA results. The 2-year outcome rates were (bottom to top): noise or rapid HR rise 0.0%, positive MTWA test 12.3%, HR <105 beats/min 14.2%, unsustained MTWA 21.8%, and excessive ventricular ectopy during exercise 27.2%. Abbreviations as in Figure 2.

the causes of indeterminate MTWA tests: HR <105 beats/min in 96 participants, ventricular ectopy in 60, unsustained MTWA in 19 (i.e., patient factors), and noise or too-rapid rise in HR in 12 (technical factors). Figure 3 shows Kaplan-Meier plots illustrating the accrual of events (mortality or non-fatal SVA) for each cause of indeterminate MTWA tests. In participants with an indeterminate MTWA test due to patient factors—HR <105 beats/min, ventricular ectopy, or unsustained MTWA—the event rate exceeded that in the group of patients with a positive test. None of the patients with an indeterminate MTWA test due to technical factors had a primary end point during 2 years of follow-up.

With a Cox model to compare indeterminate MTWA tests with positive tests, the hazard ratio was 1.3 (95% CI 0.9 to 1.7). Comparing MTWA tests classified as indeterminate owing to patient factors with positive tests, hazard ratios ranged from 1.1 to 1.6. These results demonstrate that indeterminate MTWA tests predict the primary end point as well as positive tests.

Sixty-nine patients had an ICD implanted during 2 years of follow-up: in 13% of patients with a negative test, 13% of those with a positive test, and 12% of those with an indeterminate test. Eleven patients had a non-fatal SVA as their end point. All 11 patients had ICDs, and these events were adjudicated by reviewing electrograms associated with ICD shocks. Among these 11 patients, 2 had negative MTWA tests, 5 had positive tests, and 4 had indeterminate tests.

DISCUSSION

In our study of MTWA in left ventricular dysfunction, “indeterminate” MTWA tests predicted mortality or SVA at least as well as positive tests. Ninety-four percent of tests classified as indeterminate by the Cambridge Heart D10 computer algorithm were judged by 2 expert readers to be indeterminate owing to patient factors, and these patients had a prognosis as poor as patients with positive tests. The principal clinical utility of MTWA testing lies in its ability to identify, among patients with left ventricular dysfunction and eligible for ICD prophylaxis, a subgroup at low risk of mortality or SVA. Our findings suggest that both “positive” and “indeterminate” MTWA test results indicate high risk and only patients with a negative MTWA test are low risk and therefore unlikely to benefit from ICD prophylaxis.

Indeterminate tests due to technical factors. Some investigators have argued against attributing prognostic value to these “technically inadequate” indeterminate MTWA tests, because noise does not reflect a physiologically significant risk factor (15). Although our results support that view, only 6% of our tests were judged indeterminate owing to noise or rapid HR rise. Repeating such “technically inadequate” indeterminate MTWA tests will result in a positive or negative test in about one-half of such cases, leaving very few tests that cannot be used to risk-stratify for ICD prophylaxis (12). To obtain a technically adequate MTWA test requires careful skin preparation and special electrodes to minimize noise and a HR-guided exercise protocol to prevent a too-rapid rise in HR (8,21,22).

“High-risk” indeterminate tests due to patient factors. Of the 3 patient factors that cause MTWA exercise tests to be indeterminate, 2 of them—high levels of ventricular ectopy and failure to achieve an adequate HR—were previously reported to predict poor outcome (23–29). In contrast, the development of unsustained MTWA at HR <110 beats/min was not reported previously as a marker of poor prognosis, but our results suggest that it is. An exercise test with MTWA analysis can not only provide valuable prognostic information of MTWA itself but also can reveal additional risk predictors such as exercise-induced ventricular ectopy and diminished HR response to light exercise.

Previous studies. In 2001, Tapanainen et al. (14) at Oulu University Hospital in Finland first reported that indeterminate MTWA tests predicted cardiac death in the 2 years after acute MI. A cohort of 379 consecutive patients was recruited in-hospital 7 or fewer days after acute MI. Therapy in this study was notable for lack of any revascularization (patients who had coronary artery bypass graft surgery were excluded); 97% were taking beta blocking drugs, and 46% took angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blocker (ARB) medication. MTWA tests were done 8 ± 2.4 days after the MI; the test results were: negative 38%, positive 15%, and indeterminate/incomplete 47%. Of 9 risk predictors measured in the Finnish study, indeterminate MTWA tests had the strongest association with all-cause (primary end point) or cardiac (secondary end point) death during a mean follow up of 14 ± 8 months. The MTWA tests had a negative predictive accuracy of 99%. The authors speculated on
possible reasons for the very high prevalence of indeterminate/incomplete MTWA tests, primarily the short interval after MI or the high frequency of beta blockers and ACE inhibitors or ARB medication. The MTWA test might have been done before the myocardial scar fully “matured” or before left ventricular remodeling completed. Alternatively, drug therapy, especially beta blockers, might have contributed to the large proportion of patients who did not achieve the target HR of 105 beats/min (30). Patient debility or investigator caution also might have contributed to the inadequate HR rise during exercise testing so soon after MI.

The other large post-MI study was conducted at 7 Japanese university hospitals and recruited 850 patients (31). Therapy was strikingly different from the Finnish study; 90% of the patients were revascularized, and only 13% were treated with beta blocking drugs; 18% had a LVEF <0.40. The MTWA tests were done an average of about 80 days (2.7 ± 5.4 months) after the qualifying MI; the test results were: negative 52%, positive 36%, and indeterminate/incomplete 12%. Of 11 risk predictors measured in the Japanese study, MTWA had the strongest association with arrhythmic events (sudden cardiac death, non-fatal ventricular fibrillation or tachycardia) during 25 ± 13 months of follow-up. A negative MTWA test had a negative predictive accuracy of 99%. Of 11 risk predictors, only MTWA and LVEF <0.40 were independently associated with arrhythmic events. Joint use of these 2 risk predictors improved risk stratification results. Comparing their positive predictive accuracy with that in the Finnish study, the Japanese investigators attributed the difference to performing the MTWA test too soon after MI. But, the striking differences in beta blocker use might also contribute to the differences in the test performance. Questions remain about the utility of MTWA early after MI just as questions remain about the apparent lack of ICD benefit at this stage of MI (32).

In contrast to the 2 large post-MI studies, all of the patients in our study had chronic left ventricular dysfunction with LVEF <0.41, about one-half with ischemic and one-half with nonischemic cardiomyopathy. The 49% of our patients with ischemic heart disease were enrolled as outpatients an average of 5 years after acute MI, and the 51% who had nonischemic cardiomyopathy also had longstanding left ventricular dysfunction. We had 81% of our participants taking beta blockers and 87% taking ACE inhibitors or ARB medication. Nevertheless, MTWA had good positive predictive accuracy and outstanding negative predictive accuracy (97.5%) during 20 ± 6 months of follow up. Excellent predictive accuracy in a group of patients, 81% of whom were taking beta blockers, suggests that the major differences between the Finnish and Japanese studies are predominantly due to the time after MI that the MTWA tests were done, with beta blocker treatment being less important. Reduced positive predictive accuracy for MTWA tests done in the first 2 weeks does not pose a problem for the clinical utility of MTWA. Microwatt T-wave alternans is currently used primarily to identify, among patients who have a MADIT-II (3) or SCD HeFT (Sudden Cardiac Death in Heart Failure Trial) (33) indication for ICD prophylaxis, a low-risk subgroup that is unlikely to benefit from an ICD implant. Given the results of DINAMIT (Defibrillator in Acute Myocardial Infarction Trial) (32), there is no imperative to risk stratify post-MI patients during the first 40 days after MI. Also the negative predictive accuracy of MTWA tests is 99% even in the 1st week after MI.

MTWA testing in a clinical setting. In a 2005 meta-analysis of MTWA, Gehi et al. (15) noted that “[w]hether . . . an indeterminate MTWA assessment should be considered abnormal or excluded altogether remains a methodological issue.” Hohnloser et al. (6) studied 129 MADIT-II–like patients and found that both indeterminate and positive MTWA tests identified patients at high risk of arrhythmic events, whereas patients with negative MTWA tests were at low risk and therefore unlikely to benefit from ICD prophylaxis. Our 549-patient study strongly supports Hohnloser’s recommendation that, on the basis of their association with substantially increased risk, indeterminate MTWA tests be grouped with positive tests in a single “not negative” or “abnormal” category, for the purpose of clinical decision-making and for use in epidemiologic studies or clinical trials. This clarification of how to manage patients with indeterminate MTWA tests presents clinicians with another convenience in identifying patients who are likely or unlikely to benefit from ICD prophylaxis. Our study also showed that MTWA test interpretations made by the Cambridge Heart D10 computer algorithm with no physician over-read had excellent predictive accuracy and that patients can continue their chronic medications, including beta blockers, during MTWA testing without compromising its diagnostic accuracy.

Conclusions. In patients with left ventricular dysfunction, an “indeterminate” MTWA test due to ventricular ectopy, unsustained MTWA, or low HR predicted death or SVA as well as a positive test. Conversely, a negative MTWA result was associated with a very low risk of death or SVA. These findings indicate that it is appropriate to combine “indeterminate” with positive MTWA results, yielding a single, high-risk “abnormal” group and a very low-risk normal group. In the clinical setting, this will refine the process of identifying patients likely or unlikely to benefit from ICD prophylaxis and will help doctors and patients to make more informed decisions about ICD prophylaxis.
REFERENCES


