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Microvolt T-Wave Alternans and the Risk of Death or Sustained Ventricular Arrhythmias in Patients With Left Ventricular Dysfunction

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OBJECTIVES This study hypothesized that microvolt T-wave alternans (MTWA) improves selection of patients for implantable cardioverter-defibrillator (ICD) prophylaxis, especially by identifying patients who are not likely to benefit.

BACKGROUND Many patients with left ventricular dysfunction are now eligible for prophylactic ICDs, but most eligible patients do not benefit; MTWA testing has been proposed to improve patient selection.

METHODS Our study was conducted at 11 clinical centers in the U.S. Patients were eligible if they had a left ventricular ejection fraction (LVEF) ≤0.40 and lacked a history of sustained ventricular arrhythmias; patients were excluded for atrial fibrillation, unstable coronary artery disease, or New York Heart Association functional class IV heart failure. Participants underwent an MTWA test and then were followed for about two years. The primary outcome was all-cause mortality or non-fatal sustained ventricular arrhythmias.

RESULTS Ischemic heart disease was present in 49%, mean LVEF was 0.25, and 66% had an abnormal MTWA test. During 20 ± 6 months of follow-up, 51 end points (40 deaths and 11 non-fatal sustained ventricular arrhythmias) occurred. Comparing patients with normal and abnormal MTWA tests, the hazard ratio for the primary end point was 6.5 at two years (95% confidence interval 2.4 to 18.1, $p < 0.001$). Survival of patients with normal MTWA tests was 97.5% at two years. The strong association between MTWA and the primary end point was similar in all subgroups tested.

CONCLUSIONS Among patients with heart disease and LVEF ≤0.40, MTWA can identify not only a high-risk group, but also a low-risk group unlikely to benefit from ICD prophylaxis. (J Am Coll Cardiol 2006;47:456–63) © 2006 by the American College of Cardiology Foundation

Patients with impaired left ventricular ejection fraction (LVEF) have an increased risk of sudden death, even on optimal medical therapy, and many of these deaths are attributed to sustained ventricular arrhythmias. Implantable cardioverter-defibrillators (ICDs) effectively prevent death from ventricular arrhythmias (1–5), but, unfortunately, most patients with left ventricular dysfunction who die from ventricular arrhythmias die with their first cardiac arrest (6,7). To bring the benefit of ICD therapy to patients who have not yet had episodes of sustained ventricular arrhythmias requires identification of patients at substantial risk of life-threatening arrhythmic events.

During the past 10 years, several randomized controlled trials demonstrated benefit for ICD prophylaxis in selected patients. In 2002, the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) and, in 2005, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) demonstrated that ICD prophylaxis can improve survival in patients selected primarily by a substantially reduced LVEF (8,9). However, the absolute benefit of ICD prophylaxis on mortality is relatively small (5.6% or 7.2%) in patients selected using LVEF (10). Thus, only a few of the ICDs implanted prophylactically ever deliver appropriate therapy. The Center for Medicare and Medicaid Services (CMS) has accepted the scientific validity of these ICD prophylaxis trials, but has recognized the need for better risk stratification (11) because the inconvenience, adverse effects, and cost of implanting ICDs in all patients who meet the MADIT II or SCD-HeFT criteria are substantial (10,12).

Microvolt T-wave alternans (MTWA) testing can identify patients at increased risk for sudden cardiac death.

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Abbreviations and Acronyms

CI	= confidence interval
CMS	= Center for Medicare and Medicaid Services
ICD	= implantable cardioverter-defibrillator
LVEF	= left ventricular ejection fraction
MADIT	= Multicenter Automatic Defibrillator Implantation Trial
MTWA	= microvolt T-wave alternans
NYHA	= New York Heart Association
SCD-HeFT	= Sudden Cardiac Death in Heart Failure Trial

Animal (13) and human studies (14–22) demonstrated a strong association between MTWA and increased risk of ventricular tachyarrhythmias and sudden cardiac death. While the early studies evaluated patients with a history of prior arrhythmias (14–16), only three small clinical studies have evaluated patients without prior arrhythmic events who are eligible for prophylactic ICDs (17,18,21). Remarkably, the survival of patients with a normal MTWA in these studies was excellent (corresponding to a very low false negative rate) (16–22). Accordingly, we designed and conducted a large, prospective, multicenter study supported by the National Institutes of Health to test the hypothesis that in patients with either ischemic heart disease or non-ischemic cardiomyopathy and LVEF ≤0.40, an abnormal MTWA would be associated with an increased risk of death and non-fatal arrhythmic events, and a normal MTWA would be associated with an excellent prognosis.

METHODS

Patient selection. After a pilot feasibility phase of this study at a single center and after receiving funding from the National Heart, Lung, and Blood Institute, our epidemiologic study was conducted at 11 clinical centers in the U.S. These centers represented a mixture of large community-based cardiology private practices, academic heart failure centers, and academic cardiology practices. The institutional review board at each clinical center approved the protocol, and written informed consent was obtained from all patients before their enrollment. The first patient was enrolled in November 1996 and the last in March 2003. Patients were eligible to participate if they were at least 18 years of age, had an LVEF ≤0.40, had no history of sustained ventricular arrhythmia, and gave informed consent. Because MTWA can only be measured during a regular atrial rhythm, patients who had persistent atrial fibrillation or flutter or required ventricular pacing at the time of MTWA testing were excluded. Patients with unstable coronary artery disease, with New York Heart Association (NYHA) functional class IV heart failure, or who were unable to exercise on a bicycle or treadmill also were excluded from the study. During the baseline visit, a medical history and a 12-lead electrocardiogram were obtained.

MTWA testing. Patients had an MTWA exercise test (bicycle or treadmill) while taking their regular cardiovascular medications, including beta-blockers. Careful skin preparation including mild abrasion and high-resolution electrodes (High-Res, Cambridge Heart, Inc., Bedford, Massachusetts) were used to minimize noise. Electrocardiographic leads were placed at the standard 12-lead positions and in an orthogonal X, Y, and Z configuration. Measurements were made with CH2000 or Heartwave systems (Cambridge Heart, Inc.) and utilized a spectral method of analysis designed to allow detection of alternans in the microvolt range of amplitude (14). The MTWA test was automatically interpreted within the CH2000 or the Heartwave systems by the Alternans Report Classifier (Version D10) and classified according to previously described criteria: MTWA is positive if the onset heart rate is ≤110 beats/min, negative if the maximum negative heart rate is ≥105 beats/min, and all others are indeterminate (23). Less than 10% of the tests classified as indeterminate were indeterminate because of technical issues (e.g., noise); the vast majority (>90%) of indeterminate tests were indeterminate due to physiologic reasons (ectopy, non-sustained T-wave alternans, or an inability to achieve a heart rate of 105 beats/min) (24). Because previous studies showed that positive and indeterminate MTWA tests have similar event rates (20,23), all comparisons in this analysis were made between patients with normal (negative) and abnormal (positive or indeterminate) MTWA tests.

Follow-up. The first scheduled follow-up visit occurred one month after the MTWA test. After that, patients were followed every four months. Follow-up visits focused on reviewing patients' interim medical and cardiovascular drug histories.

End points. As specified in the protocol, all end points were adjudicated by an independent external events committee, which was unaware of the MTWA test results and which utilized the modified Hinkle-Thaler classification (25) for the cause of death that was used in MUSTT (5). The events committee reviewed the primary end point forms that included a narrative of the event and other data, as specified in the protocol, pertaining to the event. The primary end point used in this study included all-cause mortality (as recommended by a policy statement on end points for trials that include ICDs written by the North American Society for Pacing and Electrophysiology) and non-fatal sustained ventricular arrhythmias (including ICD shocks with intracardiac electrograms documenting rapid ventricular tachycardia or ventricular fibrillation).

Statistical analyses. We classified MTWA tests as normal (negative) or abnormal (positive or indeterminate). Patient data were censored on the date of heart transplantation or last follow-up. The time course of the primary end point, stratified by the results of MTWA, was estimated by the Kaplan-Meier method. The association between MTWA and the primary end point was assessed using Kaplan-Meier product-limit estimates of the survival functions and tested using a log-rank test (26). 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) (27). Corresponding analyses using Cox regression were performed taking account of the effect that potential confounding variables may have on the relationship between MTWA results and the primary end point. The study protocol specified seven potential confounding variables: age, gender, etiology of heart disease (ischemic vs. non-ischemic cardiomyopathy), diabetes, and three measures of heart failure severity at the time of enrollment: NYHA functional class, LVEF, and previous hospital admission for heart failure. We adjusted for these variables by including each of them individually and collectively as independent variables in Cox proportional hazards regression models along with MTWA (27). All statistical tests were two-tailed and used an alpha level ≤ 0.05.

RESULTS

Recruitment. Our study enrolled 587 patients, but 38 of these subsequently had a post-enrollment exclusion (patients who consented to be in the study but withdrew or died before MTWA testing). Nearly all of the patients were recruited as outpatients; 49% were recruited from academic heart failure centers, 27% from community-based large general cardiology private practices, and 24% from other academic cardiology groups.

Baseline characteristics. The clinical characteristics of the 549 patients in this study are listed in Table 1; the mean age was 56 years, 71% were men, 28% had a QRS duration >120 ms, and the average LVEF was 0.25. One-half of the patients had ischemic heart disease, and the average time from their myocardial infarction was ~5 years. Two-thirds of the patients had NYHA functional class II or III heart failure, and more than one-half of the patients had a prior admission for heart failure. More than 80% were treated with a beta-blocker and an angiotensin-converting enzyme inhibitor or angiotensin II-receptor blocker. There were few substantial differences between the normal and abnormal MTWA groups (Table 1).

Primary outcome. Figure 1 shows accrual of the 51 primary end points (40 deaths and 11 non-fatal sustained ventricular arrhythmias all of which were appropriate ICD shocks for rapid ventricular arrhythmias) over two years of follow-up (mean follow-up of 20 ± 6 months). An MTWA test was done at baseline and was abnormal in 66% of participants. The two-year actuarial event rate was 15.0% in the patients with an abnormal MTWA test and 2.5% in those with a normal test (hazard ratio 6.5, 95% CI 2.4 to 18.1, $p < 0.001$). Only four events occurred in patients with

Table 1. Baseline Characteristics for All 549 Patients and for the Subgroups With Normal and Abnormal Microvolt T-Wave Alternans

Characteristic	All (n = 549)	Microvolt T-Wave Alternans		p Value*
		Normal (n = 189)	Abnormal (n = 360)	
Age, yrs	56 ± 10	53 ± 9	57 ± 10	<0.0001
Male	71	63	75	<0.01
White race	53	53	52	0.79
Ischemic cardiomyopathy	49	50	48	0.71
Hypertension	54	46	58	<0.01
Current smoker	12	14	10	0.23
Diabetes mellitus	30	30	30	0.85
Previous myocardial infarction	45	44	45	0.92
CABG surgery before enrollment	27	24	29	0.29
Previous admission for CHF	58	52	60	0.09
New York Heart Association CHF class				
No prior CHF	18	20	18	0.55
NYHA class I	16	17	16	
NYHA class II	43	45	42	
NYHA class III	22	19	24	
Left ventricular ejection fraction	0.25 ± 0.06	0.26 ± 0.07	0.25 ± 0.06	0.45
QRS duration >120 ms	28	21	31	<0.01
Drugs at enrollment				
Beta-blocker	81	88	78	<0.01
ACE inhibitor/ARB	87	85	88	0.52
Diuretic	72	69	73	0.38
Digoxin	50	41	55	<0.01
Anti-lipid	49	55	46	<0.05

All numbers in the table are percentages except for age and LVEF. *p values for continuous variables are based on *t* tests; p values for categorical variables are based on chi-square tests.

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

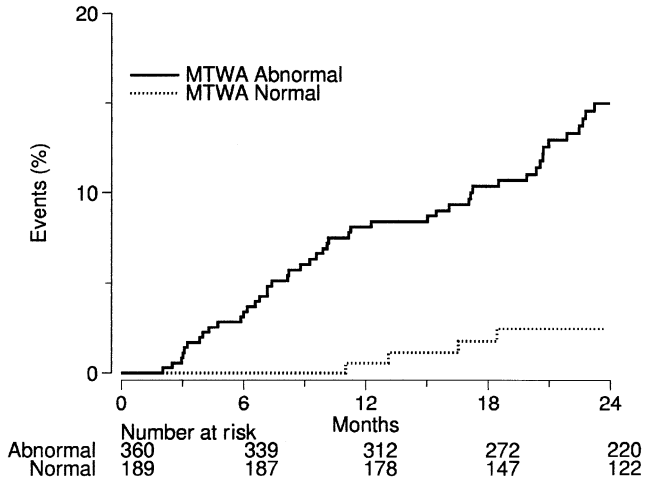

Figure 1. Kaplan-Meier mortality curves for patients with normal versus abnormal microvolt T-wave alternans (MTWA) test results. In two years of follow-up, only 4 events occurred in the 189 patients with a normal MTWA test; 47 events occurred in the group with an abnormal MTWA test. Abnormal MTWA tests comprise positive tests (n = 162, two-year event rate 12.3%) and indeterminate tests (n = 198, two-year event rate 17.5%).

a normal MTWA test: one arrhythmic death, one non-cardiac death, and two non-fatal sustained ventricular arrhythmias.

ICD implants. There were 69 patients who had ICD implants (8 before and 61 after enrollment); the actuarial two-year implant rate was 14.0% in patients with a normal MTWA test and 13.6% in those with an abnormal test. Of the ICD implants, 77% were implanted prophylactically (79% in those with a normal MTWA test and 76% in those with an abnormal test).

Other risk predictors. Table 2 compares the strength of association between MTWA and the primary outcome with other risk predictors, using univariate hazard ratios as the measure. The only other variables with hazard ratios >2.0 were gender, history of hospital admission for heart failure, and beta-blocker treatment. All of the other variables in Table 2 had hazard ratios <2.0 and were not statistically significant, although several had borderline significance (i.e., p values between 0.05 and 0.10). We adjusted MTWA results for each of the covariates tabulated in Table 2; in no instance did adjustment reduce the hazard ratio for MTWA below 6. Adjusted for the seven pre-specified variables simultaneously (see Methods section), the hazard ratio for MTWA was 5.5 (95% CI 2.0 to 15.3, p = 0.001).

Interaction of MTWA with other risk predictors. Table 3 summarizes our search for interactions between MTWA and the other variables listed in Table 2. We found no

Table 2. Kaplan-Meier Event Rates and Hazard Ratios for Risk Predictors

Variable	N	2-Year Event Rate	Hazard Ratio (95% CI)	p Value*
MTWA				
Abnormal	360	15.0		
Normal	189	2.5	6.53 (2.35–18.11)	<0.001
Age (yrs)				
≥65	126	16.0		
<65	421	9.0	1.59 (0.88–2.84)	0.120
Gender				
Male	390	12.9		
Female	159	5.3	2.67 (1.20–5.93)	0.016
Race				
White	289	11.2		
Non-white	260	10.1	1.13 (0.65–1.96)	0.670
Cardiomyopathy				
Ischemic	267	12.6		
Non-ischemic	282	8.9	1.38 (0.79–2.40)	0.254
Past CHF admission				
Yes	310	14.9		
No	229	5.1	3.12 (1.56–6.23)	0.001
NYHA functional class				
II to III	358	12.7		
<II	191	6.8	1.78 (0.93–3.41)	0.079
LVEF				
<0.31	405	12.0		
0.31 to 0.40	144	7.3	1.81 (0.88–3.73)	0.105
QRS duration				
>120 ms	150	14.0		
≤120 ms	394	9.2	1.64 (0.93–2.91)	0.088
Beta-blockers				
No	100	27.2		
Yes	434	6.8	4.24 (2.43–7.40)	<0.001

*p values are based on Wald's test using estimates from the Cox models.

CI = confidence interval; CHF = congestive heart failure, event rate percent of participants who experienced all-cause mortality and/or non-fatal sustained ventricular arrhythmias; LVEF = left ventricular ejection fraction; MTWA = microvolt T-wave alternans; NYHA = New York Heart Association.

significant interactions, indicating that MTWA was an excellent risk predictor in all of these subgroups (i.e., has significant predictive value in both categories of each variable).

Remarkably, in this sample of patients with LVEF ≤0.40, adjusting for LVEF did not add significantly to the prognostic information provided by MTWA. When MTWA and LVEF were forced into a multivariate Cox model, MTWA remained a strong, independent predictor of the primary end point (multivariate hazard ratios: MTWA 6.3, $p < 0.001$, and LVEF 1.8; $p = 0.14$). As seen in Table 3, patients with a normal MTWA test and LVEF ≤0.30 had a lower two-year actuarial event rate (3.5%) than patients with an abnormal MTWA test and an LVEF between 0.31 and 0.40 (11.8%).

DISCUSSION

This study strongly suggests that MTWA testing can identify a large group of patients with left ventricular dysfunction (LVEF ≤0.40) who have an excellent prognosis and are unlikely to benefit from ICD prophylaxis. One-third of the patients with left ventricular dysfunction re-

Table 3. Interactions between Microvolt T-Wave Alternans and Other Risk Predictors

Variable	N	MTWA	N	2-Year Event Rate	Hazard Ratio (95% CI)	p* Value
Age, yrs						
≥65	126	Abnormal	93	20.1		
		Normal	33	3.7	5.9 (0.8–44.7)	
<65	421	Abnormal	266	13.0		0.949
		Normal	155	2.2	6.4 (2.0–21.0)	
Gender						
Male	390	Abnormal	270	17.4		
		Normal	120	2.8	6.6 (2.0–21.2)	
Female	159	Abnormal	90	7.8		0.767
		Normal	69	1.9	4.5 (0.5–37.3)	
Race						
White	289	Abnormal	188	15.3		
		Normal	101	3.2	4.7 (1.4–15.7)	
Non-white	260	Abnormal	172	14.5		0.436
		Normal	88	1.4	11.9 (1.6–88.5)	
Cardiomyopathy						
Ischemic	267	Abnormal	173	16.8		
		Normal	94	4.8	3.7 (1.3–10.5)	
Nonischemic	282	Abnormal	187	13.3		0.03
		Normal	95	0.0	—†	
Previous CHF admission						
Yes	310	Abnormal	213	20.1		
		Normal	97	3.6	6.3 (2.0–20.5)	
No	229	Abnormal	141	7.5		0.927
		Normal	88	1.2	5.7 (0.7–44.9)	
NYHA functional class						
II to III	358	Abnormal	238	17.7		
		Normal	120	2.9	6.6 (2.0–21.3)	
<II	191	Abnormal	122	9.8		0.979
		Normal	69	1.5	6.4 (0.8–49.5)	
LVEF						
<0.31	405	Abnormal	271	16.1		
		Normal	134	3.5	5.0 (1.8–14.1)	
0.31 to 0.40	144	Abnormal	89	11.8		0.167
		Normal	55	0.0	—†	
QRS duration						
>120 ms	150	Abnormal	111	17.1		
		Normal	39	5.3	3.2 (0.7–13.9)	
≤120 ms	394	Abnormal	244	13.6		0.319
		Normal	150	1.7	9.2 (2.2–38.4)	
Beta-blockers						
No	100	Abnormal	77	30.6		
		Normal	23	15.8	2.2 (0.7–7.5)	
Yes	434	Abnormal	272	10.8		0.098
		Normal	162	0.6	16.1 (2.2–118.4)	

*p value for testing the equality of hazard ratios is based on Wald's test of the interaction between each variable and MTWA, except for LVEF and cardiomyopathy, which are based on likelihood ratio tests. All tests are based on Cox models.
†Indeterminate because there were no events in this group.
Abbreviations as in Table 2.

cruited for this study were classified as low risk by a normal MTWA test, and their survival rate at two years was 97.5%. The sample size of this study was large enough to allow physicians to reassure patients with left ventricular dysfunction and a normal MTWA test that their chance of experiencing either death or a sustained ventricular arrhythmia in the next two years is <5%, regardless of their LVEF, etiology of their cardiomyopathy, age, gender, diabetes, or severity of heart failure. These data extend our initial findings from the subset of patients in this study that met the MADIT II criteria (19).

This natural history study was not complicated by ICD implants during the two-year follow-up. Fewer than 15% of the patients had ICD implants. This low implant rate simplifies interpretation of our results. The implant rate was almost identical in the normal and abnormal MTWA groups (14.0% vs. 13.6%), and, in both groups, about three-fourths of the implants were prophylactic. Thus, there was equal opportunity to observe sustained ventricular arrhythmias in both groups, avoiding a potential source of bias. Importantly, appropriate ICD discharges for rapid ventricular arrhythmias were a component of the primary end point of this study; only two patients with a normal T-wave alternans test had an appropriate ICD shock in two years of follow-up.

The results reported here are consistent with previous small studies of MTWA in patients with left ventricular dysfunction and either ischemic or non-ischemic cardiomyopathy. A meta-analysis (20) that included 129 MADIT II-like patients from two other observational studies (17,18) reported no sudden cardiac death or cardiac arrest during two years of follow-up of patients with a normal MTWA test, compared with a 15.6% event rate among patients with an abnormal test (20). Most studies of non-ischemic cardiomyopathy report a very low event rate in patients with a normal MTWA test, although these studies were much too small to be definitive (21,22,28).

The MTWA was originally developed in an era where implantation of ICDs was restricted to patients with documented prior sustained ventricular arrhythmias (4,5). During this period, the preliminary focus of risk stratification was on the positive predictive accuracy of diagnostic tests used to identify patients at the highest risk of sudden cardiac death (such as electrophysiologic testing). This approach sacrificed sensitivity for specificity and failed to identify a large number of patients at risk for sudden cardiac death. This approach was also not effective for patients with non-ischemic cardiomyopathy. Even in ischemic heart disease, the negative predictive accuracy of this approach was considered unacceptable—12% of patients with a normal electrophysiology study had a sustained ventricular arrhythmic event or arrhythmic death during two years of follow-up (5).

The MADIT II and SCD-HeFT trials markedly increased the number of patients with left ventricular dysfunction for which implantation of a prophylactic ICD is indicated and reimbursed by CMS (8,9,11). The beauty of these two studies is that they both selected patients for ICD prophylaxis based on a simple, non-invasive, and widely available diagnostic assessment of LVEF. Unquestionably, both studies established a survival benefit for ICD prophylaxis in patients with left ventricular dysfunction. However, the absolute risk reduction in these two large studies was small. The MADIT II trial showed a 5.6% reduction over an average follow-up of 20 months; SCD-HeFT found a 7.2% reduction at five years of follow-up. Accordingly, roughly 18 or 14 ICDs must be implanted to save one life, but this modest benefit needs to be balanced with the risk of ICD-related adverse events (29,30) and the impact of an ICD on the quality of life (31–33). Previous studies demonstrate that ICD therapy can decrease quality of life due to a variety of problems (31–33). In addition, the economic burden is significant not only for the patient unnecessarily treated with an ICD, but also for society at large when treating so many patients who will not use their ICDs. With these issues in mind, the results of the MADIT II and SCD-HeFT trials motivate a search for patients who are unlikely to benefit from ICD prophylaxis.

The recent recall of defective ICDs has heightened public awareness to these issues. In our opinion, MTWA testing may be useful to physicians and patients who are struggling with a decision about replacing a potentially defective prophylactic ICD. For example, a normal MTWA may tip the risk-benefit balance in favor of a decision not to change an ICD that has a low failure rate. Alternatively, an abnormal MTWA may support a more confident decision to replace an ICD.

The decision by CMS to cover the cost of an ICD in all patients who meet the SCD-HeFT criteria will allow physicians to judge who should or should not have ICD prophylaxis. But how are physicians to select patients? Microvolt T-wave alternans testing is an excellent method for identifying a subset of patients with left ventricular dysfunction who are unlikely to experience sustained ventricular tachyarrhythmias and, therefore, unlikely to benefit from ICD prophylaxis.

The MTWA is a simple, relatively inexpensive, non-invasive test that can be done routinely in a doctor's office using modifications of currently available exercise testing equipment. Two other practical advantages of MTWA testing were found in this study. First, the interpretation of the MTWA tests was generated automatically by the computer algorithm in the machine without physician over read. Second, MTWA testing was an excellent risk predictor even though we conducted the test without withholding drugs. Our study showed that MTWA had excellent positive and negative predictive accuracy even in patients taking beta-blockers. These features of testing add substantially to the practicality and convenience of testing in busy office practices. If MTWA testing were used to exclude a low-risk subset of the large population of patients with left ventricular dysfunction, about two-thirds of patients would get

prophylactic ICD therapy, but those who did not would have minimal risk of experiencing ICD-preventable death. Using this strategy, among the patients with an abnormal MTWA test, only about seven ICDs would have to be implanted to save one life.

There are several limitations to this study. First, it excluded patients with persistent atrial fibrillation from the study because MTWA cannot be reliably measured during this rhythm. Second, the study excluded patients unable to exercise on a bicycle or treadmill, although MTWA can be measured during atrial pacing or potentially during a pharmacologic stress test (14,34). Finally, this study does not provide prognostic information beyond two years after the MTWA test. While the negative predictive value of an MTWA test was excellent for the two years after the test, we cannot predict how long a single normal MTWA test predicts a very low rate of death or sustained ventricular arrhythmias. Beyond two years after the MTWA test, an unknown proportion of patients with a normal T-wave alternans test may convert to an abnormal T-wave alternans status with much greater risk. Further studies are needed to evaluate this possibility and the potential utility of serial MTWA testing.

Conclusions. Among patients with left ventricular dysfunction, MTWA was able to identify not only a high-risk group but also a low-risk group, likely to survive two or more years without experiencing death or sustained ventricular arrhythmia. Importantly, because the positive and negative predictive accuracy of MTWA were similar in patients with ischemic heart disease and in those with (non-ischemic) cardiomyopathy, clinicians can feel comfortable using MTWA to select patients for ICD prophylaxis without concern for the etiology of left ventricular dysfunction. Furthermore, MTWA tests are convenient, relatively inexpensive, and safe (non-invasive).

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APPENDIX

For a list of the Data Coordinating Center and Research Holter Laboratory, the Independent External Events Committee, and the MTWA in CHF investigators, please see the online version of this article.