

A Comparison of T-Wave Alternans, Signal Averaged Electrocardiography and Programmed Ventricular Stimulation for Arrhythmia Risk Stratification

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OBJECTIVES	The goal of this study was to compare T-wave alternans (TWA), signal-averaged electrocardiography (SAECG) and programmed ventricular stimulation (EPS) for arrhythmia risk stratification in patients undergoing electrophysiology study.
BACKGROUND	Accurate identification of patients at increased risk for sustained ventricular arrhythmias is critical to prevent sudden cardiac death. T-wave alternans is a heart rate dependent measure of repolarization that correlates with arrhythmia vulnerability in animal and human studies. Signal-averaged electrocardiography and EPS are more established tests used for risk stratification.
METHODS	This was a prospective, multicenter trial of 313 patients in sinus rhythm who were undergoing electrophysiologic study. T-wave alternans, assessed with bicycle ergometry, and SAECG were measured before EPS. The primary end point was sudden cardiac death, sustained ventricular tachycardia, ventricular fibrillation or appropriate implantable defibrillator (ICD) therapy, and the secondary end point was any of these arrhythmias or all-cause mortality.
RESULTS	Kaplan-Meier survival analysis of the primary end point showed that TWA predicted events with a relative risk of 10.9, EPS had a relative risk of 7.1 and SAECG had a relative risk of 4.5. The relative risks for the secondary end point were 13.9, 4.7 and 3.3, respectively ($p < 0.05$). Multivariate analysis of 11 clinical parameters identified only TWA and EPS as independent predictors of events. In the prespecified subgroup with known or suspected ventricular arrhythmias, TWA predicted primary end points with a relative risk of 6.1 and secondary end points with a relative risk of 8.0.
CONCLUSIONS	T-wave alternans is a strong independent predictor of spontaneous ventricular arrhythmias or death. It performed as well as programmed stimulation and better than SAECG in risk stratifying patients for life-threatening arrhythmias. (J Am Coll Cardiol 2000;36:2247-53) © 2000 by the American College of Cardiology

Accurate identification of patients at increased risk for sustained ventricular arrhythmias is critical for the development of effective strategies to prevent sudden cardiac death. Traditionally, left ventricular ejection fraction and measures of ambient arrhythmia were used to identify high-risk

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cohorts and to evaluate the utility of the prophylactic administration of antiarrhythmic drugs (1). Unfortunately, this strategy has not proven beneficial in reducing mortality

(2-5). Recently, programmed ventricular stimulation during electrophysiology (EPS) testing (6,7), but not signal averaged electrocardiography (SAECG) (8), identified a cohort with left ventricular dysfunction who had improved survival with implantable cardioverter-defibrillator (ICD) placement. However, programmed stimulation is invasive and costly. Accordingly, improved noninvasive markers of arrhythmia vulnerability are needed. In this regard, T-wave alternans (TWA) is a promising new technique (9).

T-wave alternans is a heart rate-dependent measure of repolarization (10). Previously, TWA induced with atrial pacing was shown to predict ventricular arrhythmias in patients undergoing EPS (11). Subsequently, techniques were developed to allow assessment of alternans noninvasively with exercise. There is a high concordance between exercise-induced and pacing-induced TWA (12). Moreover, TWA measured noninvasively predicts the induction of ventricular tachyarrhythmias at EPS (13) as well as appropriate discharges in patients with ICDs (14). However, the predictive value of TWA measured noninvasively in patients undergoing arrhythmia evaluation is unknown.

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Abbreviations and Acronyms

EPS	= programmed ventricular stimulation during electrophysiology study
ICD	= implantable cardioverter-defibrillator
SAECG	= signal averaged electrocardiogram
TWA	= T-wave alternans
VTE	= ventricular tachyarrhythmic event

Accordingly, this study was a prospective evaluation of the role of TWA in predicting spontaneous ventricular arrhythmias in a large cohort undergoing EPS. In addition, a comparison of TWA with SAECG and programmed stimulation was performed.

METHODS

Patient population. This was a prospective, multicenter study of 337 patients undergoing diagnostic electrophysiology studies. Patients were considered for inclusion if they were in normal sinus rhythm and capable of bicycle exercise. Beta-adrenergic blocking agents were withheld for at least 24 h before the study to reduce the risk of an inadequate heart rate response with exercise. Twenty-four patients were excluded from analysis because of protocol violations (for example, electrophysiology studies or TWA not performed, TWA testing performed after electrophysiologic testing, beta-blockers not withheld). Thus, data are presented on the cohort of 313 patients enrolled in this trial without a protocol violation. Informed consent was obtained from each patient, and the study was approved by the institutional review boards of the participating institutions.

TWA measurement. T-wave alternans testing was conducted before EPS. Careful skin preparation including mild abrasion and high resolution electrodes (High-Res, Cambridge Heart, Inc., Bedford, Massachusetts) were used to minimize noise. T-wave alternans was measured during submaximal bicycle exercise to achieve a heart rate of 105 to 110 beats/min. Electrocardiographic leads were placed at the standard 12-lead positions and in an orthogonal X,Y,Z configuration. Measurements were made with the CH2000 system (Cambridge Heart, Inc., Bedford, Massachusetts) and utilized a spectral method of analysis designed to allow detection of alternans in the microvolt range of amplitude. T-wave alternans was prospectively defined as positive (TWA+) when it was sustained with an onset heart rate ≤ 110 beats per minute with an alternans amplitude $\geq 1.9 \mu V$ and alternans ratio ≥ 3 in the vector magnitude lead, any orthogonal lead or two consecutive precordial leads. T-wave alternans was prospectively defined as negative (TWA-) if the criteria for a positive test were not met and if no significant alternans was present for a 1 min period while the heart rate was greater than or equal to 105 beats/min, and the tracing was not obscured by noise or ectopic beats. Otherwise, the TWA test was considered indeterminate. T-wave alternans tests were read and interpreted by two

independent physician readers blinded to the patient's clinical data. The concordance rate between readers was 97% for determinate tests.

Signal averaged electrocardiography. Signal averaged electrocardiography was performed in the supine resting position before EPS. Time domain analysis was performed on signals from orthogonal leads using LP-Pac Q software (Arrhythmia Research Technology, Inc., Austin, Texas). The duration of signal collection was determined automatically to reduce mean noise levels to $<0.5 \mu V$. The results were considered indeterminate if the unfiltered QRS duration was >120 ms with or without bundle branch block or if a low noise recording could not be achieved. For interpretable studies, the SAECG was considered positive if two or three of the standard measurements of the filtered signal were abnormal: the QRS duration >114 ms, the root mean square voltage of the terminal 40 ms of the QRS $<20 \mu V$ or the duration of the terminal QRS less than $40 \mu V >38$ ms.

Programmed ventricular stimulation. The EPS was performed in subjects in the supine, mildly sedated, postabsorptive state by standard techniques. Programmed ventricular stimulation was performed using a stimulus duration of 2-ms at an amplitude of two to three times the diastolic threshold. The stimulation protocol consisted of up to two or three extrastimuli delivered from the right ventricular apex and outflow tract at two drive cycle lengths. The number of extrastimuli employed and detailed protocol used was individualized at each center. However, for patients with a history of ventricular tachyarrhythmias, three extrastimuli were required. The end point of EPS was the induction of sustained monomorphic ventricular tachycardia (>30 s in duration or associated with hemodynamic compromise requiring earlier intervention) or the completion of the stimulation protocol. The induction of ventricular fibrillation was defined prospectively as an indeterminate result.

Assessment of spontaneous ventricular arrhythmias. Clinical follow-up was obtained at regular intervals. The primary end point was the occurrence of a ventricular tachyarrhythmic event (VTE), which was defined prospectively as sudden cardiac death (15), sustained ventricular tachycardia, ventricular fibrillation, appropriate ICD therapy for a ventricular tachyarrhythmia or cardiac arrest. Of note, 79 patients received ICDs in this cohort, and all such devices had stored electrograms to aid in the evaluation of therapy. The secondary end point of this study was a ventricular tachyarrhythmic event or all-cause mortality. All potential end point events were classified blindly by an independent committee with no knowledge of the results of previous testing.

Statistical analysis. All results are expressed as mean \pm standard deviation. Proportions were compared with the Fisher exact test, and continuous variables were compared with the Student *t* tests. Kaplan-Meier methods were used to estimate the cumulative percentage of patients surviving

Table 1. Clinical Features of the Patient Population and the Ventricular Arrhythmia Subgroup

	All Patients	Ventricular Arrhythmia Subgroup
n	313	215
Age (yrs)	56 ± 16	60 ± 14
Gender (% male)	64	75
Coronary artery disease (%)	41	55
Congestive heart failure (%)	34	45
Ejection fraction	0.44 ± 0.18	39 ± 18

free from end point events over time. For the estimates of survival free from VTE, follow-up data were censored at the time of cardiac surgery (other than coronary artery bypass surgery), myocardial infarction or initiation or discontinuation of Vaughn Williams class I or III antiarrhythmic drugs. Censoring for changes of antiarrhythmic drug use was performed in 22 patients (7.6%) at a follow-up of 195 ± 126 days. For analysis of survival free from VTE plus death, there was no censoring of follow-up data. Comparisons between the survival curves were made using the log-rank statistic. All follow-up data were censored at 400 days. Survival probabilities and relative risks for the Kaplan-Meier analyses were evaluated at 400 days of follow-up.

Stepwise Cox regression methods were used to examine the association of risk factors with the time to first occurrence of end point events during 400 days of follow-up. The following variables were included in the analysis: TWA, SAECG, EPS, age, gender, left ventricular ejection fraction, coronary artery disease, nonischemic dilated cardiomyopathy, diabetes, history of revascularization and history of sustained ventricular arrhythmia. Subgroup analysis was performed on the prospectively defined cohort with known or suspected ventricular arrhythmias. A p value <0.05 (two-tailed) was considered statistically significant for all analyses.

RESULTS

Patient population. There were 313 patients evaluated in this study. The mean age of this cohort was 56 ± 16, and the mean left ventricular ejection fraction was 44% ± 18%. In 34% of patients there was a history of congestive heart failure, including 22% with New York Heart Association

class II symptoms and 12% with class III symptoms. There was no structural heart disease in 30% of the cohort. At baseline evaluation 5.8% of patients were receiving class I antiarrhythmic drugs, and 5.4% were receiving class III drugs.

The most frequent indication for EPS was syncope or presyncope (41%). The other indications included cardiac arrest in 5% of patients, sustained ventricular tachycardia in 14% and nonsustained ventricular tachycardia in 4%. An additional 31% of patients were being evaluated for the diagnosis or treatment of supraventricular arrhythmias. Since the clinical utility of risk stratification will be restricted to those patients with known or suspected ventricular arrhythmias, this cohort was identified prospectively for subgroup analysis. Clinical features of the full study population and of the ventricular arrhythmia subgroup are shown in Table 1.

Outcomes of TWA, SAECG and EP tests. For this cohort the results of TWA were positive in 31% of patients, negative in 45% and indeterminate in the remaining 24%. Indeterminate results were due primarily to the inability to achieve the target heart rate or to frequent ectopy. The SAECG was positive (abnormal) in 19% of patients, negative in 56% and indeterminate in the remaining 25%. Indeterminate results were due primarily to a prolonged QRS duration (>120 ms) or to excess noise. Finally, the results of programmed ventricular stimulation were positive for the induction of sustained monomorphic ventricular tachycardia in 22% of patients, negative in 60% and indeterminate in the remaining 18%. Indeterminate results were due primarily to the induction of ventricular fibrillation or to protocol violations. Each of the three tests had roughly equivalent rates of indeterminacy.

Noninvasive test predictors of programmed stimulation. The SAECG and TWA testing of patients occurred before EPS. In 129 patients there were determinate TWA, SAECG and programmed stimulation results. The statistical performance of the noninvasive tests in this subgroup of patients are summarized in Table 2. The relative risk of TWA for predicting EP outcome was 5.7 (p < 0.0001).

The SAECG was a less sensitive but more specific test than TWA for predicting EP outcome in this population (Table 2), suggesting that these two noninvasive tests may be complementary to predict the results of electrophysiology testing. To assess this possibility, the performance of com-

Table 2. Statistical Performance of the Noninvasive Tests to Predict the Results of EPS

	Sensitivity	Specificity	PPV	NPV	Relative Risk	p Value
TWA	77.8%	72.5%	42.9%	92.5%	5.7	< 0.0001
SAECG	55.6%	83.3%	46.9%	87.6%	3.8	< 0.0001
TWA+SAECG+	48.1%	96.1%	76.5%	87.5%	6.1	< 0.0001
TWA+SAECG-	29.6%	76.5%	25.0%	80.4%	1.3	0.6170
TWA-SAECG+	7.4%	87.3%	13.3%	78.1%	0.6	0.7360
TWA-SAECG-	14.8%	40.2%	6.2%	64.1%	0.2	< 0.0001

EPS = programmed ventricular stimulation during electrophysiology study; NPV = negative predictive value; PPV = positive predictive value; SAECG = signal averaged electrocardiogram; TWA = T-wave alternans.

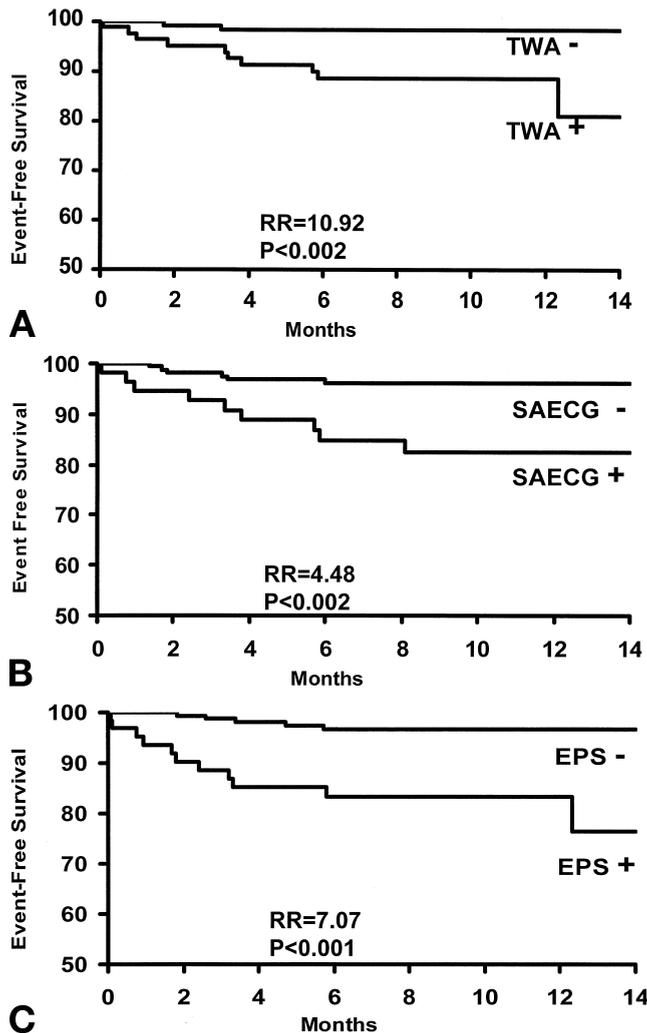


Figure 1. Risk stratification of ventricular tachyarrhythmic events. Kaplan-Meier survival curves are shown for each of the three tests evaluated. **A:** T-wave alternans; **B:** Signal averaged electrocardiography; **C:** Programmed ventricular stimulation. EPS = programmed ventricular stimulation during electrophysiology study; SAECG = signal averaged electrocardiogram; TWA = T-wave alternans.

binations of TWA and SAECG to predict EPS outcomes were calculated. In each case a given noninvasive test result (e.g., TWA+SAECG+) is compared with the three other possible results (Table 2). Patients in whom both tests were abnormal (i.e., TWA+SAECG+) had a high likelihood of having inducible ventricular tachycardia, as reflected by a higher specificity (96%) and negative predictive value (88%). However, this group had a lower sensitivity (48%) than TWA alone. Conversely, TWA- SAECG- had a low sensitivity (15%) and positive predictive value (6%) for inducible ventricular tachycardia but also had a lower specificity (40%) than TWA alone. Outcomes with discordant noninvasive results (i.e., TWA+SAECG- and TWA- SAECG+) were less predictive of EPS.

Risk stratification of spontaneous arrhythmias. Follow-up was obtained in 290 patients with a mean duration of 297 ± 103 days. There were 22 VTE, the primary end point for this study (see Methods section),

Table 3. Event-free Survival at 400 Days for Different Combinations of TWA and SAECG Outcomes

	VTE End Point	VTE or Death End Point
TWA+SAECG+	67.7%	67.7%
TWA+SAECG-	97.3%	93.6%
TWA-SAECG+	100%	100%
TWA-SAECG-	97.4%	97.5%

SAECG = signal averaged electrocardiogram; TWA = T-wave alternans; VTE = ventricular tachyarrhythmic event.

including 15 in patients with ICDs. These included five patients with sudden death and 17 nonfatal arrhythmias. The Kaplan-Meier curves of event-free survival are shown in Figure 1. All three tests significantly discriminated patients for events. The data for TWA are shown in Panel A. Patients who were TWA+ had an almost 11-fold increased risk of experiencing an event compared with patients who were TWA- ($p < 0.002$). The probability of not experiencing a tachyarrhythmic event at 400 days in the TWA+ group (i.e., event-free probability) was 0.81, while it was 0.98 in the TWA- group. The ventricular tachyarrhythmia event-free survival curves for SAECG (Panel B) and EPS (Panel C) also demonstrate an early and persistent separation between groups. However, the relative risks of these tests were less than they were for TWA. The results of EPS had a relative risk of 7.1 ($p < 0.001$), while the relative risk for the SAECG was 4.5 ($p < 0.002$).

There were 27 secondary end points (VTE or all-cause mortality) including 10 deaths for this study. Again, of the three tests evaluated, TWA risk-stratified the population most accurately with a relative risk of 13.9 ($p < 0.001$). The EPS had a relative risk of 4.7 ($p < 0.001$) to discriminate patients with this end point, while the SAECG had a relative risk of 3.3 ($p < 0.007$).

To evaluate the utility of using both noninvasive tests to predict spontaneous events, survival analysis was performed for the primary and secondary end points on all 155 patients with follow-up data and determine TWA and SAECG tests. Four groups were compared in this analysis (TWA+SAECG+, TWA+SAECG-, TWA-SAECG+ and TWA-SAECG-). There were 9 primary end points (VTE events) in this group and 10 secondary end points (VTE or death). The 400-day event-free survival rates are listed in Table 3. The TWA+SAECG+ group had a markedly lower event-free survival rate than that of any of the other groups.

Ventricular arrhythmia subgroup analyses. The ventricular arrhythmia subgroup was constructed by excluding those patients referred for evaluation of supraventricular arrhythmia. The majority of these patients (60%) were referred for the evaluation of syncope or presyncope, with an additional 6% referred for nonsustained ventricular tachycardia. Only 27% had a prior history of sustained ventricular arrhythmia. Other demographic characteristics for the subgroup are shown in Table 1. The results from the Kaplan-Meier

Table 4. Event-free Survival at 400 Days Stratified by Test and Clinical Characteristics for the Subgroup With Known or Suspected Ventricular Arrhythmias

	Number of Events	Relative Risk	Log-rank p Value	Probability of Survival (Positive)	Probability of Survival (Negative)
VTE End point					
TWA	12	6.1	< 0.029	78.8%	96.6%
EP	15	4.6	< 0.009	76.7%	95.0%
SAECG	15	3.4	< 0.01	77.5%	93.4%
VTE or Death					
TWA	15	8.0	< 0.004	74.1%	96.8%
EP	19	2.9	< 0.038	75.4%	91.5%
SAECG	17	2.5	< 0.035	78.4%	91.4%

EP = programmed ventricular stimulation during electrophysiology; SAECG = signal averaged electrocardiogram; TWA = T-wave alternans; VTE = ventricular tachyarrhythmic event.

analysis are presented in Table 4. The TWA test had the highest relative risks for both end points: 6.1 ($p < 0.029$) for the VTE end point and 8.0 ($p < 0.004$) for the VTE or death end point. The Kaplan-Meier curves of TWA for the ventricular arrhythmia subgroup are shown in Figure 2.

Predictors of clinical events. To assess the independent predictors of clinical events, multivariate analysis was performed to evaluate the influence of factors on the hazard ratio (see Methods section). The end point was VTE or death (there were not enough events to evaluate the VTE end point alone). Of the clinical factors evaluated, only the ejection fraction (relative risk = 3.7, $p < 0.004$) and a history of sustained ventricular arrhythmia (relative risk = 3.8, $p < 0.001$) were univariate predictors of events. The only statistically significant independent predictors of events

were TWA (relative risk 12.2) and EPS (relative risk 3.0), which had a model chi-square of 20.6 ($p < 0.0001$). A Cox regression analysis was performed including the noninvasive predictors only (that is, excluding EPS). This analysis revealed that TWA (relative risk 10.9, model chi-square 15.5, $p < 0.0001$) was the only statistically independent predictor of events.

DISCUSSION

The major findings of this study are that TWA measured noninvasively predicts the results of programmed ventricular stimulation as well as of subsequent spontaneous arrhythmic events. Compared with SAECG, TWA was a more sensitive predictor of the induction of sustained VT during EPS, as well as a better discriminator of ventricular tachyarrhythmic events or death. Multivariate analysis showed that TWA was an independent predictor of clinical arrhythmic events and not simply a marker of left ventricular dysfunction or inducible sustained ventricular tachycardia, although the mean left ventricular ejection fraction was lower in subjects who were TWA+ compared with those who were TWA- ($35 \pm 17\%$ vs. $54 \pm 13\%$, $p < 0.001$).

Comparison with previous studies. The initial studies of microscopic TWA demonstrated that this phenomenon was a measure of arrhythmia vulnerability in animals (16,17). This measure is heart rate-dependent (10), so early studies evaluated TWA with atrial pacing. Studies in humans demonstrated that TWA is a sensitive predictor of the induction of VT (18) or of spontaneous ventricular arrhythmias (10). More recently, techniques were developed to measure TWA noninvasively with exercise, and a high concordance between exercise and pacing induced alternans was documented (12). Hohnloser and colleagues (19) showed that exercise induced TWA was a better predictor of ICD shocks than multiple other noninvasive tests, including measures of baroreflex sensitivity, ambient arrhythmias, QT dispersion and SAECG (13). This study is the largest trial to date of TWA and confirms that this test is a measure of arrhythmia vulnerability.

This study also confirms that the SAECG can identify patients with inducible VT and who are at risk for sponta-

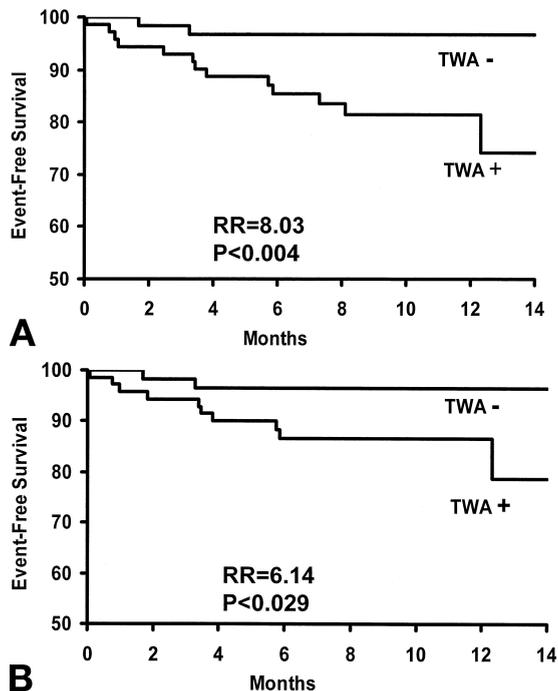


Figure 2. The role of TWA for risk stratification in patients with known or suspected ventricular arrhythmias. Kaplan-Meier survival curves are shown based on TWA results. **A:** Ventricular tachyarrhythmic events is the end point. **B:** Ventricular tachyarrhythmic events or death is the end point. TWA = T-wave alternans.

neous ventricular arrhythmias. The role of the SAECG for arrhythmia risk stratification is well established (20-22). However, in this study the SAECG did not perform as well as TWA for predicting the induction of VT or spontaneous arrhythmias. Moreover, multivariate analysis indicated that TWA, but not SAECG, was an independent predictor of subsequent clinical events. Although the SAECG was not an independent predictor of events, it may enhance the prognostic value of TWA, as suggested recently by Ikeda and colleagues (23) in a study of patients after myocardial infarction. For instance, only 6% of subjects with both tests negative (that is, TWA-SAECG-, Table 1) had inducible VT, suggesting that this group may not need to undergo invasive testing. In contrast, patients with both tests positive (TWA+SAECG+) had a more than 10-fold increased risk of a ventricular tachyarrhythmic event at 400 days compared with the other groups (Table 2), suggesting that this group should be treated aggressively.

Our experimental design is deserving of comment. Patients were recruited prospectively who were in sinus rhythm and who were undergoing electrophysiology study. This avoided any bias of primarily choosing patients who had already experienced life-threatening arrhythmias or had received defibrillators since risk stratification is not important in those subjects. In fact, only 19% of patients had a history of a sustained ventricular tachyarrhythmia in this trial. However, the inclusion of some very low-risk patients without structural heart disease may have increased the predictive value of the tests. To control for this possibility, subgroup analysis was performed on patients being evaluated for known or suspected ventricular arrhythmias. T-wave alternans remained a strong predictor of clinical events in this group (Fig. 2, Table 4).

Study limitations. Our results must be interpreted in the face of certain methodologic limitations. T-wave alternans cannot be measured in all patients. Atrial fibrillation precludes the accurate assessment of TWA, SAECG and other dynamic repolarization parameters (24). T-wave alternans could not be measured in some other subjects because they could not achieve a heart rate of at least 105 beats per minute with exercise. In addition, the patient population and indications for EPS were heterogeneous, so it is possible that these results do not apply to all subgroups. Another limitation of this study is that a majority of ventricular tachyarrhythmic events were nonfatal. This study was not powered to assess the predictors of mortality only. Since all such events were confirmed to be ventricular tachyarrhythmias by a blinded, independent events committee, it is assumed that many of these arrhythmias would have been fatal in the absence of therapeutic interventions such as ICDs. Finally, beta-blockers were withheld before TWA testing was performed. This strategy may have led to inaccuracies in risk assessment although there was no difference in TWA results between patients on beta-blockers before evaluation (39% TWA+) and those not on beta-blockers (42% TWA+, $p = 0.77$).

In summary, this study demonstrates that TWA is an accurate predictor of the results of EPS and a strong independent predictor of spontaneous ventricular arrhythmias or death. It performed at least as well as EPS and better than SAECG to risk stratify patients for life-threatening arrhythmias. These results indicate that TWA should be a useful adjunct to the clinical evaluation of patients with known, suspected or at high risk for ventricular tachyarrhythmias, and it should be considered as a noninvasive method to identify high-risk subjects for future preventative trials.

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