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JOURNAL OF CARDIOVASCULAR ELECTROPHYSIOLOGY, Volume 13, No. 9, September 2002

Exercise is Superior to Pacing for T Wave Alternans Measurement in Subjects with Chronic Coronary Artery Disease and Left Ventricular Dysfunction

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Exercise vs Pacing for TWA Measurement. ***Introduction:*** **T wave alternans (TWA) is a heart rate-dependent marker of vulnerability to ventricular arrhythmias. Atrial pacing and exercise both are used as provocative stimuli to elicit TWA. However, the prognostic value of the two testing methods has not been compared. The aim of this prospective study was to compare the prognostic value of TWA measured during bicycle exercise and atrial pacing in a large cohort of high-risk patients with ischemic heart disease and left ventricular dysfunction.**

Methods and Results: **This was a prospective study of 251 patients with coronary artery disease and left ventricular dysfunction who were referred for electrophysiologic studies (EPS) for standard clinical indications. Patients underwent TWA testing using bicycle ergometry (exercise TWA, n = 144) and/or atrial pacing (pacing TWA, n = 178). The primary endpoint was the combined incidence of death, sustained ventricular arrhythmias, and appropriate implantable cardioverter defibrillator therapy. The predictive value of exercise and pacing TWA for EPS results and for endpoint events was determined. Exercise and pacing TWA both were significant predictors of EPS results (odds ratios 3.0 and 2.9 respectively, P < 0.02). Kaplan-Meier survival analysis of the primary endpoint revealed that exercise TWA was a significant predictor of events (hazard ratio 2.2, P = 0.03). In contrast, pacing TWA had no prognostic value for endpoint events (hazard ratio 1.1, P = 0.8).**

Conclusion: **TWA should be measured during exercise when it is used for clinical risk stratification. EPS results may not be an adequate surrogate for spontaneous events when evaluating new risk stratification tests.** *(J Cardiovasc Electrophysiol, Vol. 13, pp. 845-850, September 2002)*

electrophysiologic study, risk stratification

Introduction

T wave alternans (TWA) is a heart rate-dependent marker of vulnerability to ventricular arrhythmias.[1-3] It has been shown to be associated with inducible ventricular arrhythmias during electrophysiologic studies (EPS) as well as spontaneous arrhythmic events.[1,4-6] When TWA was introduced for arrhythmia risk stratification, invasive atrial pacing was used to elevate the heart rate sufficiently to permit alternans measurement.[1] Subsequently, new spatial averaging software and electrodes were developed that permitted noninvasive TWA measurement during bicycle exercise.[3-6] In one small study, exercise and pacing produced concordant TWA results.[3] However, the comparative prognostic value of exercise and pacing TWA for EPS results and subsequent spontaneous arrhythmic events has not been evaluated. We hypothesized that exercise-induced TWA would be a better predictor of arrhythmia vulnerability, because it is measured during the state of sympathetic activation and vagal withdrawal that has been implicated as a trigger for spontaneous arrhythmias.[7,8] Accordingly, the aim of the present study was to compare the prognostic value of exercise and pacing TWA prospectively in a large cohort of high-risk patients with ischemic heart disease and left ventricular dysfunction who were referred for EPS.

Methods

Patients

This was a prospective, single-center study of 251 consecutive patients at the University of Maryland Medical Center. The inclusion criteria were age >21 years, significant coronary artery disease (≥50% stenosis in any of the three major vessels), left ventricular ejection fraction ≤40%, normal sinus rhythm, and referral for EPS for standard clinical indications. The exclusion criteria were current use of Vaughan-Williams Class I or III antiarrhythmic drugs or amiodarone use for the past 3 months, New York Heart Association class IV congestive heart failure, and myocardial infarction or revascularization procedure (percutaneous coronary angioplasty, bypass surgery) within 96 hours. Written informed consent was obtained from all patients,

Dr. Rashba was supported by a Beginning Grant-in-Aid from the Mid-Atlantic Affiliate of the American Heart Association, a Passano Foundation Physician-Scientist Award, and an Intramural Grant Award from the University of Maryland School of Medicine. Dr. Gold is the recipient of an unrestricted research grant from Cambridge Heart, Inc., the manufacturer of the T wave alternans equipment.

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Manuscript received 25 March 2002; Accepted for publication 3 July 2002.

and the study was approved by the Institutional Review Board.

T Wave Alternans

TWA testing was conducted before EPS. Beta-adrenergic blockers were withheld for at least 24 hours before the study to reduce the risk of an inadequate chronotropic response to exercise or Wenckebach phenomenon during atrial pacing and because these agents reduce TWA independent of their effects on heart rate.[9,10] Careful skin preparation including mild abrasion was performed to reduce the skin-electrode impedance. Special high-resolution electrodes (High-Res™; Cambridge Heart, Inc., Bedford, MA, USA) were used to minimize noise. ECG leads were placed at the standard precordial lead positions (V_1 to V_6) and in an orthogonal X,Y,Z configuration, as described previously.[5] TWA was measured with the CH2000 system (Cambridge Heart, Inc.) and used a spectral method of analysis designed to allow detection of alternans in the microvolt range of amplitude.[1] TWA was measured using exercise in 73 patients, pacing in 107 patients, and both modalities in 71 patients. Thus, a total of 144 patients had TWA testing using exercise and 178 patients had TWA testing using pacing. The choice of testing modalities was at the discretion of the attending physician. The concordance of exercise and pacing TWA results was evaluated in the subgroup of 71 patients who underwent testing with both modalities. Exercise TWA testing was conducted before EPS using submaximal bicycle exercise to achieve a heart rate of 105 to 110 beats/min. Pacing TWA was measured during EPS after initial catheter placement and before programmed ventricular stimulation. High right atrial pacing was performed at cycle lengths of 600 msec (100 beats/min), 550 msec (109 beats/min), and 500 msec (120 beats/min). Data were acquired for a minimum of 5 minutes at each paced rate.

TWA was prospectively defined as positive (TWA+) when it was sustained for at least 1 minute with an onset heart rate $<$110 beats/min, alternans amplitude $\geq$1.9 μV, and alternans ratio (signal-to-noise ratio) $\geq$3 in the vector magnitude lead, any orthogonal lead, or two consecutive precordial leads. TWA was defined as negative (TWA$-$) if the criteria for a positive test were not met, if there was no significant alternans for 1 minute while the heart rate was $\geq$105 beats/min, and if the tracing was not obscured by noise or ectopic beats. Otherwise, TWA was considered indeterminate.[5] Data were analyzed by two experienced readers who were blinded with respect to the clinical data and the results of EPS.

Electrophysiologic Testing

Electrophysiologic testing was performed with the patient in the mildly sedated, postabsorptive state, as previously described.[11] Sinus and AV nodal function were assessed, followed by programmed ventricular stimulation at two right ventricular sites with up to three extrastimuli at two drive cycle lengths (600 and 400 msec). The endpoint of EPS was the induction of sustained monomorphic ventricular tachycardia or the induction of ventricular fibrillation with one or two extrastimuli. The induction of ventricular fibrillation with three extrastimuli was considered a negative test.[12] Implantable cardioverter defibrillators (ICDs) were placed if patients had a positive EPS test or previous sustained ventricular arrhythmias.

Endpoints

Clinical follow-up was obtained every 3 months. The primary endpoint was the combined incidence of death, appropriate ICD therapy with pacing or shocks, sustained ventricular tachycardia, or ventricular fibrillation arrest. Of note, 183 patients received ICDs in this study, and all such devices had stored electrograms to aid in the evaluation of therapy.

Statistical Analysis

All results are expressed as mean $\pm$ SD. Categorical variables were compared using the Chi-square test, and continuous variables were compared using one-way analysis of variance. Logistic regression analysis was conducted to identify predictors of EPS results, and $P < 0.05$ was considered statistically significant. Kaplan-Meier survival curves were used to estimate the cumulative percentage of patients surviving free from endpoint events over time. Comparisons between the survival curves were made using the log rank statistic. A Cox proportional hazards model was constructed to identify variables that were significantly associated with endpoint events. All variables that were significantly associated with outcome events in univariate Cox survival analyses ($P < 0.05$) were entered in a multivariate Cox proportional hazards model, and $P < 0.05$ was required to retain a variable in the model. The following variables were evaluated for Cox survival analyses: exercise TWA, pacing TWA, EPS, age, gender, race, prior coronary bypass surgery, New York Heart Association class (II/III vs I), left ventricular ejection fraction, cardiovascular medications (aspirin, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, digoxin, diuretic, statin), and history of sustained ventricular arrhythmia.

Results

Patient Population

There were 251 patients evaluated in this study. The study population had a mean age of 65 $\pm$ 10 years and a mean left ventricular ejection fraction of 27% $\pm$ 8%. All patients had significant coronary artery disease by study design, and 55% had previously undergone coronary bypass surgery. The majority of patients had symptomatic New York Heart Association class II or III heart failure (89%). EPS was performed for primary prevention purposes in 66% of patients (nonsustained ventricular tachycardia 42%, syncope 24%) and to evaluate sustained ventricular tachycardia (25%) or ventricular fibrillation arrest (9%) in the remainder. TWA was measured using exercise in 73 patients, pacing in 107 patients, and both modalities in 71 patients. There were no significant differences among these three subgroups with respect to any of the clinical characteristics that were evaluated in this study (Table 1).

Comparison of TWA Measurement Using Exercise and Pacing

The concordance of exercise and pacing TWA results was evaluated in the subgroup of 71 patients who had both tests (Table 2). The overall concordance rate of exercise

TABLE 1
Clinical Characteristics of the Study Population

	Pacing TWA (n = 107)	Exercise TWA (n = 73)	Both Modalities (n = 71)
Age (years)	66 ± 11	64 ± 10	65 ± 10
Male (%)	81	79	82
Race (%)			
Caucasian	79	82	82
African-American	21	18	18
Coronary artery bypass grafting (%)	62	47	55
New York Heart Association class (%)			
I	12	8	13
II	57	59	62
III	31	33	25
Left ventricular ejection fraction (%)	26 ± 8	28 ± 8	27 ± 7
Prior sustained ventricular arrhythmias (%)	26	42	35
Implantable cardioverter defibrillator (%)	68	71	83
Cardiovascular medications (%)			
Aspirin	73	66	80
ACE inhibitors	71	68	75
Angiotensin receptor blocker	6	10	7
Beta-blockers	68	73	79
Digoxin	43	47	58
Loop diuretic	65	64	65
Statin	48	55	62

$P > 0.05$ for comparison of the three groups for all variables.
ACE = angiotensin-converting enzyme; TWA = T wave alternans.

TWA and pacing TWA was only 55%. The concordance rates for positive, negative, and indeterminate tests were 88%, 39%, and 15%, respectively. When patients with indeterminate results on either test were excluded, the concordance rate was 73% (n = 49). Pacing TWA yielded more positive tests (73% vs 47%) and fewer indeterminate results (7% vs 27%, P = 0.02 for an overall difference in results with the two modalities).

The results of exercise and pacing TWA were compared using all patients who were tested using each modality (n = 143 and n = 178, respectively). Exercise TWA testing was positive in 49% of patients, negative in 26%, and indeterminate in 25%. Exercise TWA tests were indeterminate because of excessive ectopy in 47% of cases and because of an inadequate heart rate response in 53%. Pacing TWA testing was positive in 65% of cases, negative in 27%, and indeterminate in 8%. Pacing TWA tests were indeterminate because of excessive ectopy in 80% of cases and because 1:1 AV conduction did not persist during atrial pacing at 109 beats/min in the remaining 20%. The prevalence of indeterminate test results was significantly greater with exercise TWA (25% vs 8%, P < 0.001).

TABLE 2
Concordance of Exercise and Pacing TWA Results in Subjects Who Had Both Tests Performed (n = 71)

		Pacing TWA		
Exercise TWA	**N**	**Positive**	**Negative**	**Indeterminate**
Positive	33	29 (88)	4 (12)	0 (0)
Negative	18	9 (50)	7 (39)	2 (11)
Indeterminate	20	14 (70)	3 (15)	3 (15)

Numbers in parentheses are percentages.
TWA = T wave alternans.

Predictive Value of TWA for EPS Results

EPS testing was positive in 67% of patients; sustained monomorphic ventricular tachycardia was the induced arrhythmia in 97% of such patients. The performance of exercise TWA, pacing TWA, and clinical factors for predicting EPS results is given in Table 3. The performance of the two TWA testing modalities was similar: the odds ratio of exercise TWA for predicting EPS outcome was 3.0 (P = 0.013), and the odds ratio of pacing TWA was 2.9 (P = 0.004). Indeterminate exercise or pacing TWA results were not significantly associated with a positive EPS (odds ratios 1.6 for exercise TWA, P = 0.32; odds ratio 2.5 for pacing TWA, P = 0.15). A prior history of sustained ventricular arrhythmias and Caucasian race also were significant predictors of a positive EPS.

Predictors of Arrhythmic Events

Mean duration of follow-up was 499 ± 395 days. A total of 88 arrhythmic events occurred during follow-up, including 35 deaths, 50 episodes of ventricular tachycardia treated with antitachycardia pacing (n = 16) or shocks (n = 34), 2 episodes of spontaneous sustained ventricular tachycardia, and 1 aborted ventricular fibrillation arrest. The incidence of endpoint events was the same in the subgroups that had exercise TWA and pacing TWA (35% of patients in each group). The Kaplan-Meier curves of event-free survival for TWA are shown in Figures 1 and 2. Exercise TWA was a significant predictor of events (hazard ratio 2.2 [1.1 to 4.7], P = 0.03; Fig. 1), but pacing TWA was not useful for risk stratification (hazard ratio 1.1 [0.6 to 1.9], P = 0.8; Fig. 2). Indeterminate exercise TWA results were associated with an intermediate prognosis that did not differ significantly from TWA+ and TWA− patients (Fig. 1). Patients with positive, negative, and indeterminate pacing TWA results had a similar prognosis (Fig. 2). In univariate Cox survival

TABLE 3
Noninvasive Predictors of EPS Results

	Sensitivity	Specificity	PPV	NPV	OR (95% CI)	P Value
Exercise TWA	72%	53%	79%	45%	3.0 (1.3–7.0)	0.013
Pacing TWA	78%	45%	76%	48%	2.9 (1.4–5.8)	0.004
Prior sustained ventricular arrhythmias	43%	85%	86%	43%	4.5 (2.3–9.0)	<0.001
Caucasian race	84%	27%	70%	47%	2.0 (1.1–3.9)	0.028

CI = confidence interval; EPS = electrophysiologic studies; OR = odds ratio; PPV = positive predictive value; NPV = negative predictive value; TWA = T wave alternans.

analyses, exercise TWA, symptomatic heart failure, and a positive EPS were all associated with an increased risk for events during follow-up (Table 4). Beta-blocker treatment was associated with a reduced risk for endpoint events. The indication for EPS was not a predictor of endpoint events (hazard ratio 0.8 [0.5 to 1.3] for primary vs secondary prevention, P = 0.4). In multivariate analyses, exercise TWA was the only independent predictor of events.

All patients had TWA and EPS testing in the absence of antiarrhythmic drugs; however, some subjects were treated with Class III agents for atrial arrhythmias during follow-up (amiodarone 10%, sotalol 3%). Importantly, there was no significant difference in the incidence of endpoint events when patients who were and who were not treated with antiarrhythmic drugs were compared (40% vs 35% respectively, P = 0.7).

Discussion

The major findings of this study are that exercise TWA (and not pacing TWA) is a significant and independent predictor of events. In contrast, exercise and pacing TWA both predicted the results of EPS with similar accuracy. These results call into question the use of EPS results as a surrogate for spontaneous events during the development and validation of new risk stratification tests.

Comparison of Exercise and Pacing TWA

TWA is critically dependent on heart rate.[1-3] When the methodology for measuring microvolt levels of TWA was initially described, atrial pacing was used to elevate the heart rate sufficiently to permit TWA measurement.[1] Hohnloser et al.[3] reported that exercise and pacing TWA results were 84% concordant in a small series of patients, but subjects with indeterminate results were excluded and the comparative prognostic value of the two methods for EPS results or subsequent spontaneous arrhythmias was not examined. In the present study, the concordance rate was similar when patients who had indeterminate results with either modality were excluded (73%); however, the overall concordance rate was only 55% (Table 2). In particular, patients with negative or indeterminate exercise TWA results frequently had a positive pacing TWA test (23/38 cases). Both exercise and pacing TWA were significant predictors of EPS results, in agreement with previous reports.[1,4] However, exercise TWA (but not pacing TWA) was a significant predictor of spontaneous arrhythmic events. One potential reason for this discrepancy is suggested by the results of the recent MUSTT trial. In this study, patients with negative EPS results were followed prospectively in a registry and the combined incidence of cardiac arrest and death from arrhythmia was compared between EPS+ patients who were randomized to no antiarrhythmic therapy and the EPS− registry patients.[12] The adjusted hazard ratio associated with a positive EPS was 1.5, which is similar to the results of EPS in the present study. However, the EPS− patients remained at substantial risk for recurrent arrhythmic events (12% at 2 years, 24% at 5 years). Because EPS is an imperfect risk stratification test, it is not surprising that some predictors of EPS results are not useful for identifying patients who are vulnerable to spontaneous ventricular arrhythmias.

One limitation of our study is that the prognostic value of

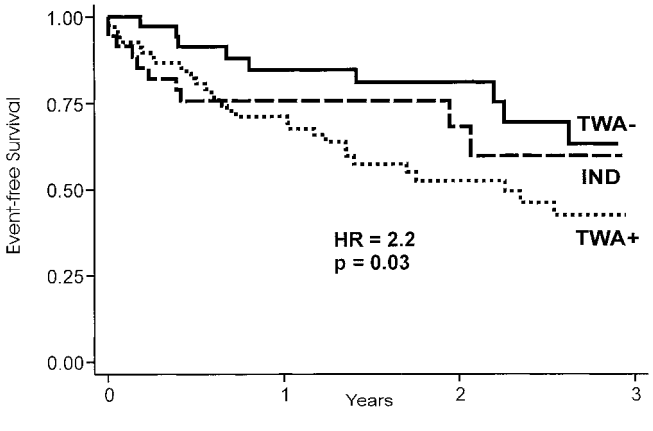

Figure 1. *Prognostic value of exercise-induced T wave alternans (TWA) for endpoint events. Kaplan-Meier curves of event-free survival are shown, truncated at 3 years. The hazard ratio (HR) for the comparison of TWA+ and TWA− patients is shown. IND = indeterminate.*

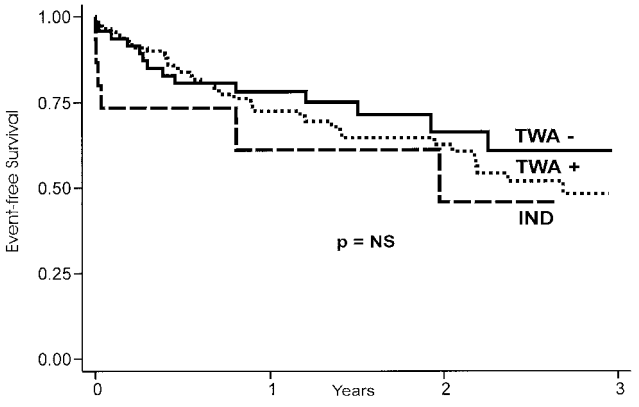

Figure 2. *Prognostic value of pacing-induced T wave alternans (TWA) for endpoint events. Kaplan-Meier curves of event-free survival are shown, truncated at 3 years. IND = indeterminate.*

TABLE 4
Predictors of Endpoint Events

	Hazard Ratio	95% CI	P Value
Exercise TWA	2.2	1.1–4.7	0.03
NYHA class II/III	2.6	1.1–5.9	0.03
EPS	1.9	1.2–3.1	0.01
Beta-blockers	0.6	0.4–0.9	0.03

CI = confidence interval; EPS = electrophysiologic studies; NYHA = New York Heart Association; TWA = T wave alternans.

exercise and pacing TWA could not be compared in the same patients, because only 49 subjects had determinate results with both testing modalities. Because the choice of testing modalities was not randomized, it is important to determine if the poor prognostic value of pacing TWA is attributable to inadvertent selection of a sicker patient subgroup that was unable to exercise. This explanation is not supported by our data, because the patients who underwent exercise TWA only and pacing TWA only did not differ significantly with respect to the incidence of endpoint events or clinical characteristics such as age, left ventricular ejection fraction, or New York Heart Association class (Table 1). We hypothesize that exercise TWA performed better because the sympathetic activation and vagal withdrawal that are characteristic of physical exercise more closely approximate the milieu that precipitates ventricular arrhythmias in the clinical setting in subjects with coronary artery disease.[7,8] Indeed, we and others previously demonstrated that acute beta-blockade markedly reduces TWA independent of heart rate effects, suggesting that the sympathetic nervous system has important influences on TWA.[9,10]

Comparison with Previous Studies

Our results must be reconciled with those of Rosenbaum et al.,[1] who reported that pacing TWA was a significant predictor of spontaneous arrhythmias. In addition, the prognostic value of exercise TWA was less in the present study than in previous reports.[5,6] The most likely explanation for these discrepancies is that previous studies of TWA enrolled all patients who were referred for EPS, including subjects without structural heart disease and other low-risk patients with relatively preserved left ventricular function and no symptoms of congestive heart failure.[1,5,6] Because patients without structural heart disease are less likely to have a positive TWA test and to have clinical arrhythmic events, the prognostic value of the test was exaggerated. In the present study, we evaluated a more homogenous group of patients with left ventricular dysfunction and coronary artery disease. Our patients had a greater incidence of clinical congestive heart failure (89% vs 45%), lower mean left ventricular ejection fractions (27% vs 39%), and more arrhythmic events (35% vs 9%) than the patients in the recent multicenter study of Gold et al.[5] Although our population consisted of sicker patients than were evaluated in previous studies of TWA, the characteristics of this cohort are similar to those of patients who were studied in previous large-scale primary prevention trials.[13,14] In the recent MADIT-2 trial, the utility of prophylactic ICD placement was evaluated in subjects with prior myocardial infarction and severe left ventricular dysfunction without additional risk stratification.[15] Although ICD placement significantly improved survival,[15] the magnitude of the mortality reduction was much less than in previous studies.[13,14] Additional studies are needed of patients who meet MADIT-2 criteria to determine if TWA can be used to identify low-risk patients who may not require prophylactic ICD placement.

Patients with indeterminate TWA results have been excluded from most previous studies of TWA.[1-6] In the present study, patients with indeterminate exercise TWA results had an intermediate prognosis compared with TWA+ and TWA− subjects. The high event rate in this subgroup may be attributable to poor functional capacity in subjects who could not achieve the target heart rate[16] or to frequent ventricular ectopy.[13,14] The high prevalence of indeterminate exercise TWA results in our cohort (25% of patients) is consistent with prior reports,[5,6,16] highlighting the need for additional studies to define the best management strategy for such patients.

It is notable that the incidence of inducible ventricular arrhythmias was higher in the present study than in previous reports.[12,14] This finding is likely attributable to the fact that our patients had a high prevalence of clinical factors that have been associated with a positive EPS (e.g., previous sustained ventricular tachycardia, male gender, previous myocardial infarction, congestive heart failure, Caucasian race).[17] Moreover, our subjects with nonsustained ventricular tachycardia were identified almost exclusively by telemetry during a hospitalization, which has been correlated with a higher inducibility rate.[18] Because TWA was a significant predictor of EPS results, the high incidence of positive TWA tests in our study may be due to the same clinical factors that predisposed to a positive EPS. In addition, we withheld beta-blockers before TWA testing because these agents reduce the magnitude of TWA independent of their effects on heart rate, resulting in a reduced sensitivity for a positive EPS.[9,10] The precise mechanisms that are responsible for gender and racial differences in arrhythmia inducibility remain poorly defined and require further study.

Study Limitations

All-cause mortality was a component of the composite endpoint for this study. Although it is possible that some of the deaths may not have been due to ventricular arrhythmias, this endpoint was prospectively chosen because of the difficulties inherent in determining cause-specific mortality in clinical trials.[19] Endpoint events more likely may have been detected in patients who underwent ICD placement because arrhythmias that may not have caused symptoms in the absence of a device were detected and treated. Programming of the ICDs also was not standardized, which may have influenced event detection. Our study population consisted of patients who were referred for primary and secondary prevention of ventricular arrhythmias. However, because the indication for EPS was not a predictor of endpoint events, it is unlikely that this factor influenced our results. Finally, our population consisted exclusively of patients with coronary artery disease, and the results may not be applicable to subjects with nonischemic dilated cardiomyopathy or other forms of structural heart disease. However, ischemic heart disease is the most common substrate among patients who are at risk for sudden cardiac death.[20,21]

Conclusion

TWA should be measured during exercise when it is used for clinical risk stratification. Pacing TWA is not useful for subjects with indeterminate exercise TWA results, because pacing TWA does not predict events. Our results suggest that EPS results are not an adequate surrogate for spontaneous events when evaluating new risk stratification tests.

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