Enhanced Detection of Arrhythmia Vulnerability Using T Wave Alternans, Left Ventricular Ejection Fraction, and Programmed Ventricular Stimulation: A Prospective Study in Subjects with Chronic Ischemic Heart Disease

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Combined Use of TWA, LVEF, and PVS. ***Introduction:*** **In previous studies, the prognostic value of T wave alternans (TWA) was similar to that of programmed ventricular stimulation (PVS). However, presently it is unclear if TWA and PVS identify the same patients or provide complementary risk stratification information. In addition, the effects of left ventricular ejection fraction (LVEF) on the prognostic value of TWA are unknown. The aim of this study was to determine if combined assessment of TWA, LVEF, and PVS improves arrhythmia risk stratification.**

Methods and Results: **This was a prospective study of 144 patients with coronary artery disease and LVEF $\leq$40% who were referred for PVS for standard clinical indications. The endpoint was the combined incidence of death, sustained ventricular arrhythmias, and appropriate implantable cardioverter defibrillator (ICD) therapy. TWA (hazard ratio 2.2, P = 0.03) and PVS (hazard ratio 1.9, P = 0.05) both were significant predictors of endpoint events, and TWA was the only independent predictor. LVEF markedly influenced the prognostic value of TWA, which was a potent predictor of events in subjects with LVEF between 30% and 40% (event rates: TWA+ 36%, TWA- 0%, P = 0.001) but did not predict events in subjects with LVEF <30% (hazard ratio 1.1, P > 0.5). PVS successfully identified additional low-risk patients within the cohort with negative or indeterminate TWA results (hazard ratio 4.7, P = 0.015) but did not provide incremental prognostic information for TWA+ patients (hazard ratio 0.9, P > 0.5).**

Conclusion: **The combined use of TWA, LVEF, and PVS is a promising new approach to arrhythmia risk stratification that permits identification of high-risk and very-low-risk patients.** *(J Cardiovasc Electrophysiol, Vol. 15, pp. 170-176, February 2004)*

T wave alternans, electrophysiologic study, risk stratification

Introduction

Sudden cardiac death remains common in the United States, with an estimated 400,000 cases reported annually.[1] Coronary artery disease is the underlying substrate in the majority of cases of sudden cardiac death.[1] The implantable cardioverter defibrillator (ICD) has been demonstrated to improve survival among patients with an aborted cardiac arrest[2] and in subjects with ischemic heart disease, left ventricular dysfunction, nonsustained ventricular tachycardia, and inducible sustained ventricular tachycardia during programmed ventricular stimulation (PVS).[3,4] 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.[5] Although ICD placement significantly improved survival,[5] the magnitude of the mortality reduction was less than in previous studies,[3,4] raising concerns about the cost effectiveness of this strategy.[6] To this end, there is great interest in developing new risk stratification tests that can successfully identify low-risk patients with ischemic heart disease and left ventricular dysfunction that may not require prophylactic ICD placement.

T wave alternans (TWA) is a promising noninvasive marker of vulnerability to ventricular arrhythmias.[7-9] It has been shown to be associated with inducible ventricular arrhythmias during PVS as well as spontaneous arrhythmic events.[7-9] In a recent multicenter trial, TWA performed as well as PVS in arrhythmia risk stratification.[8] However, presently it is unclear if TWA and PVS identify the same patients or provide complementary risk stratification information. In addition, because left ventricular ejection fraction (LVEF) has an important influence on the diagnostic performance of other risk stratification tests,[10,11] we hypothesized that LVEF also would influence the prognostic value of TWA. The aims of this prospective study were to determine if combined assessment of TWA, LVEF, and PVS improved arrhythmia risk stratification and to compare the prognostic

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value of TWA in subjects with severe (LVEF <30%) and moderate (LVEF 30%–40%) left ventricular dysfunction.

Methods

Patients

This was a prospective, single-center study of 144 patients at the University of Maryland Medical Center who were recruited over a 3-year period (1997–2000). Inclusion criteria were age >21 years, significant coronary artery disease by arteriography (≥50% stenosis in any of the three major vessels), LVEF ≤40%, normal sinus rhythm, and referral for PVS for standard clinical indications (asymptomatic nonsustained ventricular tachycardia, syncope, sustained ventricular tachycardia, ventricular fibrillation arrest). 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 (NYHA) class IV congestive heart failure, and myocardial infarction or revascularization procedure (percutaneous coronary angioplasty, bypass surgery) within 96 hours. LVEF was measured by echocardiography, radionuclide ventriculography, or contrast left ventriculography. Written informed consent was obtained from all patients, and the study was approved by the Institutional Review Board at the University of Maryland.

T Wave Alternans

TWA testing was conducted before PVS using submaximal bicycle exercise to achieve a heart rate of 105 to 110 beats/min for at least 1 minute. Beta-adrenergic blockers were withheld for at least 24 hours before the study because these agents suppress TWA and increase the number of indeterminate TWA tests due to chronotropic incompetence.[12,13] Careful skin preparation including mild abrasion was performed in order to reduce the skin-electrode impedance. Special high-resolution electrodes (High-Res^{TM}, Cambridge Heart, Inc., Bedford, MA, USA) were used to minimize noise. ECG leads were placed at the standard precordial lead positions (V_1–V_6) and in an orthogonal X, Y, Z configuration, as described previously.[8] TWA was measured with the CH2000 system (Cambridge Heart, Inc., Bedford, MA, USA) using a spectral method of analysis designed to allow detection of alternans in the microvolt range of amplitude.[7]

TWA was prospectively defined as positive when it was sustained for at least 1 minute with an onset heart rate <110 beats/min, alternans amplitude ≥1.9 μV, and alternans ratio (signal-to-noise ratio) ≥3 in the vector magnitude lead, any orthogonal lead, or two consecutive precordial leads (TWA+). TWA was defined as negative if the criteria for a positive test were not met, if there was no significant alternans for 1 minute while the heart rate was ≥105 beats/min, and if the tracing was not obscured by noise and had <10% ectopic beats (TWA-). Otherwise, TWA was considered indeterminate.[8] Data were analyzed by two experienced readers who were blinded with respect to the clinical data and the results of PVS.

Electrophysiologic Testing

Electrophysiologic testing was performed in the mildly sedated, postabsorptive state, as previously described.[14] Sinus and AV nodal function were assessed, followed by PVS at two right ventricular sites with up to three extrastimuli at two drive cycle lengths (600 ms, 400 ms). The endpoint of PVS was induction of sustained monomorphic ventricular tachycardia with up to three extrastimuli or induction of ventricular fibrillation with one or two extrastimuli. Induction of ventricular fibrillation with three extrastimuli was considered a negative test.[15] ICDs were placed if patients had a positive PVS 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 for ventricular arrhythmias with pacing or shocks, sustained ventricular tachycardia, or ventricular fibrillation arrest. Follow-up was terminated if a patient had an endpoint event. The same composite endpoint was used for all patients, because it is well recognized that the ICD does not provide complete protection from arrhythmic death.[16] The endpoints were determined by an investigator who was blinded with respect to the TWA and PVS results. All ICD therapies were classified as appropriate or inappropriate (e.g., atrial arrhythmias, noise) based on analysis of stored intracardiac electrograms. Of note, 111 subjects received ICDs in this study (77% of patients), and all such devices had stored electrograms to aid in the evaluation of therapy.

Statistical Analysis

All results are expressed as mean ± SD. Categorical variables were compared using the Chi-square test, and continuous variables were compared using *t*-tests or one-way analysis of variance. 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. The following variables were included in the analysis: TWA, PVS, age, gender, race, prior coronary bypass surgery, NYHA class (II/III vs I), left ventricular ejection fraction, and history of sustained ventricular arrhythmia. Testing was performed to detect significant interactions between TWA and other study variables ($P < 0.05$ for interaction term). When significant interactions were detected, separate analyses were performed for TWA among subjects with and without the risk factor. The incidence of endpoint events and the sensitivity, specificity, positive predictive value, and negative predictive value of risk stratification tests were calculated at 2-year follow-up. Hazard ratios were calculated using all available follow-up. Separate analyses were conducted in the primary prevention subgroup that was referred for evaluation of asymptomatic nonsustained ventricular tachycardia or syncope. Because arrhythmias detected by the ICD were a component of the composite endpoint for this study, it is possible that patients with ICDs may have been more likely to have endpoint events. For this reason, the prognostic value of TWA and other risk factors also was evaluated in the subgroup with ICDs because the ability to detect endpoint events should be more uniform within this cohort.

Subgroup analyses were conducted in subjects with determinate TWA results to determine if the prognostic value of TWA was affected by left ventricular function. The median ejection fraction in our study population was chosen a priori as a dichotomization cutpoint (30%). The predictive value of TWA for endpoint events was compared for

subjects with LVEF ≥30% (n = 55) and LVEF <30% (n = 53). Additional analyses were conducted to determine if PVS provides incremental prognostic information in patients with various combinations of TWA and LVEF results.

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 $P < 0.10$ was required to retain a variable in the model.

Results

Patient Population

One hundred forty-four patients were evaluated in this study. Mean patient age was 64 ± 10 years, and mean left ventricular ejection fraction of 28 ± 7% (Table 1). All patients had significant coronary artery disease by study design, and the majority had NYHA class II or III heart failure (90%). PVS was performed for asymptomatic nonsustained ventricular tachycardia in 37% of patients, to clarify the etiology of syncope in 24%, to evaluate previous documented sustained monomorphic ventricular tachycardia in 32%, and for ventricular fibrillation arrest in 7% of cases. When the clinical characteristics of subjects with LVEF ≥30% and LVEF <30% were compared, women were more likely to have LVEF ≥30% (28% vs 10%, P = 0.01). However, there were no significant differences between the two LVEF subgroups with respect to any other clinical factors, including age, NYHA class, TWA results, PVS results, ICD use, or cardiovascular medication use (Table 1).

Results of TWA and PVS

TWA was positive in 70 patients (49%), negative in 38 (26%), and indeterminate in 36 (25%). TWA tests were indeterminate because of excessive ectopy in 49% of cases and because of an inadequate heart rate response in 51%. PVS was positive in 100 patients (70%). Sustained monomorphic ventricular tachycardia was the induced arrhythmia in 97% of PVS+ patients. As expected, patients with previously documented sustained ventricular arrhythmias were more likely to have a positive PVS (odds ratio 4.2 [1.8–9.8], P = 0.006). TWA (odds ratio 3.0 [1.3–7.0], P = 0.01) and Caucasian race (odds ratio 2.8 [1.2–6.7], P = 0.02) also were significant predictors of PVS results.

Predictors of Endpoint Events

Mean duration of follow-up was 509 ± 387 days. A total of 50 events occurred during follow-up (35% of patients), including 14 deaths and 36 episodes of ventricular tachycardia treated with antitachycardia pacing (n = 10) or shocks (n = 26). There were seven events among patients who did not receive ICDs (all deaths). TWA was a significant predictor of events (event rates: TWA+: 40% TWA-: 16%, hazard ratio 2.2, P = 0.03). Patients with indeterminate TWA results had an intermediate prognosis that did not differ significantly from that of TWA+ and TWA- patients (25% event rate). PVS also was a significant predictor of endpoint events (event rates: PVS+: 35% PVS-: 18%, hazard ratio 1.9, P = 0.05). There was a nonsignificant trend for LVEF <30% to be associated with endpoint events (event rates: LVEF <30%: 35%, LVEF ≥30%: 25%, hazard ratio 1.5, P = 0.14). Kaplan-Meier curves of event-free survival for TWA and

TABLE 1
Clinical Characteristics of the Study Population

	LVEF <30% (n = 68)	LVEF ≥30% (n = 76)	All Patients (n = 144)
Age (years)	65 ± 10	64 ± 10	64 ± 10
Male (%)*	90	72	81
Race (%)			
Caucasian	82	82	81
African-American	18	18	19
Coronary artery bypass grafting (%)	50	52	51
New York Heart Association Class (%)			
I	7	13	10
II	62	59	60
III	31	28	30
Prior sustained ventricular arrhythmias (%)	40	38	39
Inducible ventricular arrhythmias (%)	72	67	69
T wave alternans (%)			
Positive	54	43	49
Negative	26	26	26
Indeterminate	19	30	25
Implantable cardioverter defibrillator (%)	78	76	77
Cardiovascular medications (%)			
Aspirin	72	74	73
Angiotensin-converting enzyme inhibitors	78	66	72
Angiotensin receptor blocker	7	9	8
Beta-blockers	72	79	76
Digoxin	57	47	52
Loop diuretic	68	62	65
Statin	62	55	58

*P = 0.01, LVEF ≥30% vs LVEF <30%.

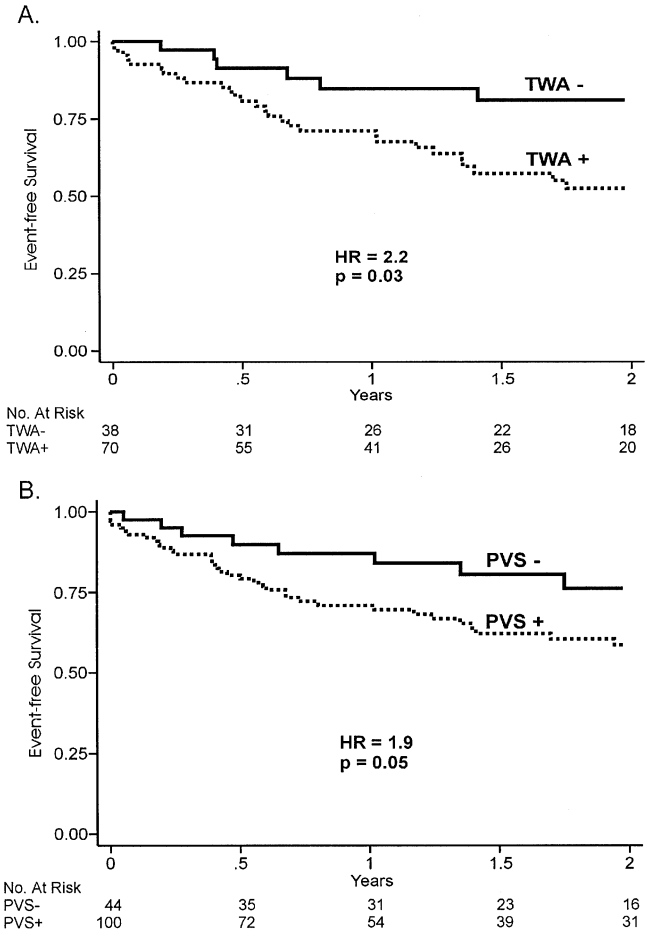

Figure 1. *Risk stratification for endpoint events. Kaplan-Meier curves of event-free survival are shown, truncated at 2 years. A: T wave alternans B: Programmed ventricular stimulation. PVS = programmed ventricular stimulation during electrophysiologic studies; TWA = T wave alternans.*

PVS are shown in Figure 1. In multivariate analyses, TWA was the only independent predictor of events. The incidence of endpoint events did not differ significantly among subjects who were referred for nonsustained ventricular tachycardia (32%), syncope (34%), or prior documented sustained ventricular arrhythmias (38%). A significant interaction was present between TWA and LVEF ($P < 0.001$), indicating that the prognostic value of TWA differed among patients with LVEF <30% and LVEF ≥30%. There were no significant interactions between TWA and other clinical factors such as age, gender, race, PVS results, prior coronary bypass surgery, NYHA class (II/III vs I), or indication for PVS.

Influence of LVEF on TWA Risk Predictions

In order to characterize the influence of LVEF on TWA risk predictions, the prognostic value of TWA was assessed separately in subjects with LVEF ≥30% and LVEF <30%. TWA was a highly significant predictor of events in subjects with LVEF ≥30% (event rates: TWA+ 36%, TWA- 0%, $P = 0.001$, Fig. 2A). In contrast, TWA had no prognostic value for subjects with LVEF <30% (hazard ratio 1.1, $P > 0.5$, Fig. 2B). The sensitivity, specificity, and negative predictive value of TWA were improved when testing was restricted to subjects with LVEF ≥30% (Table 2).

In the subgroup with ICDs, TWA was not a significant predictor of outcome events (hazard ratio 1.6, $P = 0.3$). However, a significant interaction between TWA and LVEF <30% also was present in the subgroup with ICDs ($P < 0.001$). In this subgroup, TWA remained a highly significant predictor of events in subjects with LVEF ≥30% (event rates: TWA+ 32%, TWA- 0%, $P = 0.008$) but did not predict events in subjects with LVEF <30% (event rates: TWA+ 45%, TWA- 50%, $P > 0.5$).

Combined Use of TWA, LVEF, and PVS to Predict Endpoint Events

Additional analyses were conducted to determine if PVS provides incremental prognostic information for patients who were identified as high risk with TWA and LVEF testing. Because patients with negative TWA results and LVEF ≥30% had an excellent prognosis (Fig. 2A), they were excluded from this analysis because no further risk stratification was necessary. The prognostic value of PVS was evaluated in the following two subgroups: (1) patients with either indeterminate TWA results ($n = 36$) or the combination of LVEF <30% and negative TWA results ($n = 18$; Fig. 3A) and (2) patients with positive TWA results ($n = 70$, Fig. 3B). In the former

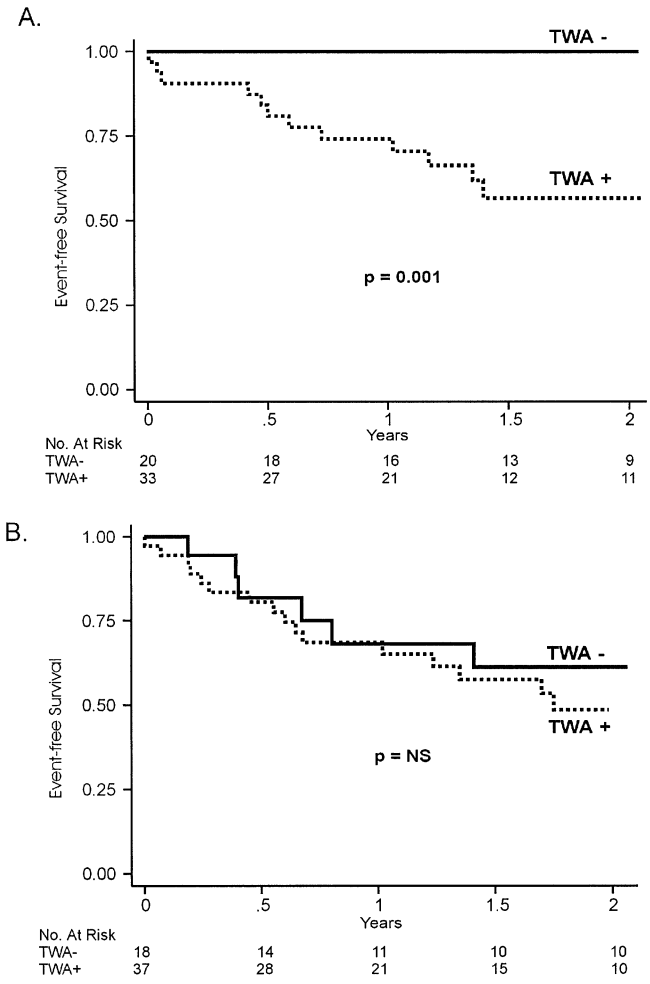

Figure 2. *Influence of left ventricular ejection fraction (LVEF) on the prognostic value of T wave alternans (TWA) for endpoint events. Kaplan-Meier curves of event-free survival are shown, truncated at 2 years. A: LVEF ≥30%. B: LVEF <30%.*

TABLE 2
Event-Free Survival at 2 Years Stratified by TWA, LVEF, and PVS Results

	HR (95% CI)	Log Rank P Value	Sensitivity	Specificity	PPV	NPV
TWA	2.2 (1.1–4.7)	0.03	82%	43%	40%	84%
PVS	1.9 (1.0–3.9)	0.05	80%	35%	35%	80%
LVEF <30%	1.5 (0.9–2.7)	0.14	56%	56%	35%	75%
TWA, if LVEF ≥30%	∞	0.001	100%	49%	36%	100%
PVS, if indeterminate TWA test or TWA- and LVEF <30%	4.7 (1.3–16.7)	0.015	88%	42%	39%	89%

CI = confidence interval; HR = hazard ratio; NPV = negative predictive value; PPV = positive predictive value; PVS = programmed ventricular stimulation during electrophysiologic studies; TWA = T wave alternans.

group, PVS successfully identified a population with a low event rate during follow-up (event rates: PVS+ 39% PVS- 6%, hazard ratio 4.7, P = 0.015, Fig. 3A). The diagnostic accuracy of PVS was improved when testing was restricted to this subgroup (Table 2). In contrast, PVS did not provide additional prognostic information in subjects with positive TWA tests (hazard ratio 0.9, P > 0.5, Figure 3B). The prognostic value of PVS in subjects with positive TWA tests was unchanged when the subgroups with LVEF <30% and LVEF ≥30% were analyzed separately.

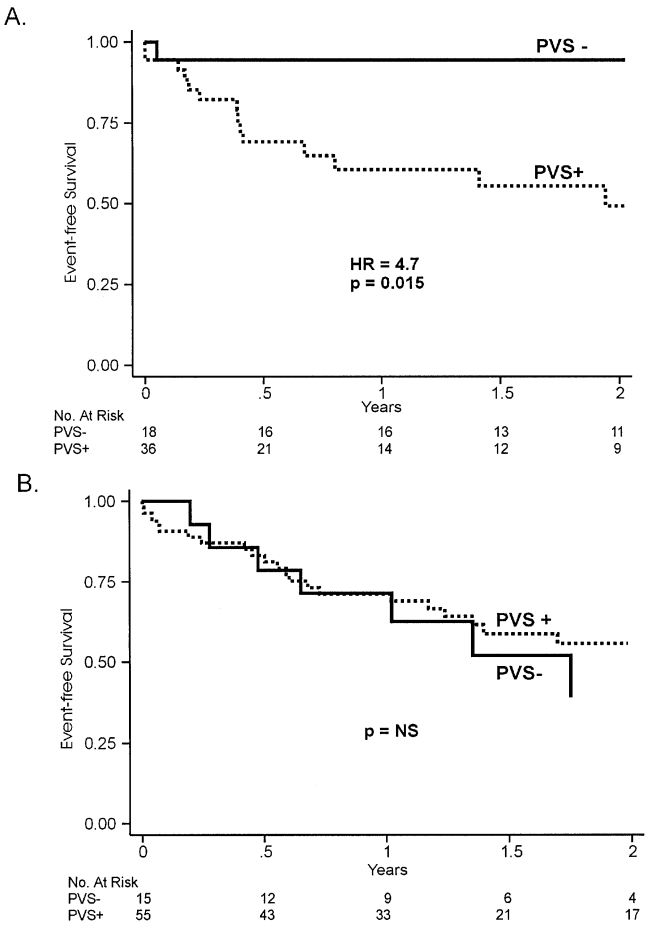

Figure 3. *Prognostic value of PVS for endpoint events in patients with various combinations of T wave alternans (TWA) and left ventricular ejection fraction (LVEF) results. A: Patients with indeterminate TWA results or having both negative TWA results and LVEF <30%. B: Patients with positive TWA results. Kaplan-Meier curves of event-free survival are shown, truncated at 2 years. PVS = programmed ventricular stimulation during electrophysiologic studies.*

Subgroup Analysis Among Primary Prevention Patients

In the primary prevention subgroup, TWA was not a significant predictor of outcome events (hazard ratio 1.8, P = 0.2). However, a significant interaction between TWA and LVEF <30% also was present in primary prevention patients (P < 0.001). In this subgroup, TWA remained a highly significant predictor of events in subjects with LVEF ≥30% (event rates: TWA+ 47%, TWA- 0%, P = 0.006) but did not predict events in subjects with LVEF <30% (event rates: TWA+ 33%, TWA- 35%, hazard ratio 0.7, P > 0.5, Figure 4). PVS successfully identified additional low-risk patients within the cohort with negative or indeterminate TWA results (event rates: PVS+ 32% PVS- 6%, hazard ratio 3.7, P = 0.05) but did not provide incremental prognostic information for TWA+ patients (event rates: PVS+ 38%, PVS- 47%, hazard ratio 0.9, P > 0.5).

Discussion

The major findings of this study are that combined assessment of TWA, LVEF, and PVS identified a cohort that had a very low incidence of events during follow-up. Patients who were TWA- and had LVEF ≥30% had no events during the 2-year follow-up (Fig. 2). In addition, PVS was useful for identifying low-risk patients within the cohort with either indeterminate TWA results or the combination of LVEF <30% and negative TWA results (Fig. 3). In contrast, if either TWA or PVS was used as the only risk stratification test, an appreciable proportion of the patients with negative test results remained at risk for events (Fig. 1). Our results have important implications for the development of new strategies to reduce the incidence of sudden cardiac death by targeting ICD placement to those individuals who are most susceptible to malignant ventricular arrhythmias.

Several previous studies demonstrated that TWA is a potent predictor of PVS results and that both TWA and PVS predict arrhythmic events during follow-up.[7,8] These data formed the rationale for the ongoing Alternans Before Cardioverter-Defibrillator (ABCD) trial, which is evaluating whether TWA is equivalent to PVS for predicting arrhythmic events after initial ICD placement. The obvious question is whether TWA should simply supplant PVS if equivalence is demonstrated in the ABCD trial. In this regard, our study is the first to specifically examine whether TWA and PVS identify the same patients or provide complementary risk stratification information. Our results suggest that TWA

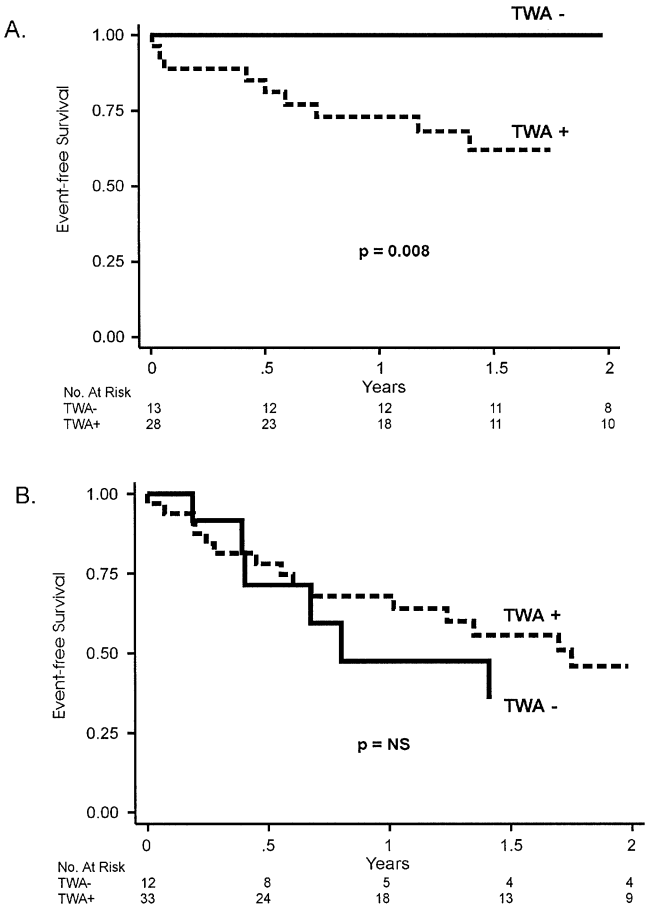

Figure 4. *Influence of left ventricular ejection fraction (LVEF) on the prognostic value of T wave alternans (TWA) for endpoint events, in the primary prevention subgroup. Kaplan-Meier curves of event-free survival are shown, truncated at 2 years. A: LVEF ≥30%. B: LVEF <30%.*

testing provides an acceptable negative predictive value among patients with moderate left ventricular dysfunction (LVEF 30%–40%), but that negative results on both tests are needed to achieve an acceptable negative predictive value among sicker patients with severe left ventricular dysfunction (LVEF <30%). Because the magnitude of left ventricular dysfunction correlates with a more adverse prognosis,[17] the most likely explanation for our findings is the well-known inverse relationship between negative predictive value and the incidence of outcome events.[18] In other words, as the incidence of outcome events increases, it becomes increasingly difficult to identify low-risk patients with any risk stratification test. Hohnloser et al.[19] recently reported on 129 patients who met MADIT-2 criteria in a retrospective analysis from two previously published clinical trials. The negative predictive value of TWA was 94.3%, which is better than the negative predictive value of TWA in the present study (84%). The most likely explanation for this discrepancy is that our patients had a higher incidence of outcome events (35% vs 24%), which had the expected effects on the negative predictive value of TWA.

Patients with indeterminate TWA results have been excluded from most previous studies of TWA.[7-9] In the present study, patients with indeterminate TWA results had an intermediate prognosis compared with TWA+ and TWA- subjects. The events in this subgroup may be attributable to poor functional capacity in subjects who could not achieve the target heart rate[13] or to frequent ventricular ectopy.[3,4] Importantly, we demonstrated that PVS is a potent predictor of events in subjects with indeterminate TWA results (Fig. 3A).

It is notable that the incidence of inducible ventricular arrhythmias was higher in the present study than in previous reports.[3,4] This finding likely is attributable to the fact that our patients had a high prevalence of clinical factors that have been associated with a positive PVS (e.g., previous sustained ventricular tachycardia, male gender, previous myocardial infarction, congestive heart failure, Caucasian race).[20] 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.[21] Because TWA was a significant predictor of PVS results, the high incidence of positive TWA tests in our study may be due to the same clinical factors that predisposed to a positive PVS. In addition, we withheld beta-blockers prior to 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 PVS.[12]

In any observational study, it is important to determine if interactions are present between the risk predictors of interest and other variables, such as clinical factors. When significant interactions are present, the stratum-specific effects provide the best characterization of the predictive value of a risk stratification test. A significant interaction between TWA and LVEF was present in the overall study cohort, the primary prevention subgroup, and the subgroup with ICDs. The overall predictive value of TWA is a composite of the effects in the two LVEF subgroups. Because the predictive value of TWA was so markedly different in subjects with LVEF ≥30% and LVEF <30%, it is not surprising that TWA was not a significant predictor in ICD patients or primary prevention patients when the TWA-LVEF interaction was not taken into account.

Study Limitations

The composite endpoint for this study is subject to some limitations. Although some of the deaths may not have been due to ventricular arrhythmias, this endpoint was used because of the difficulties inherent in determining cause-specific mortality in clinical trials.[22] Patients who underwent ICD placement may have been more likely to have endpoint events detected because arrhythmias that may not have caused symptoms in the absence of a device were detected and treated. The programming of the ICDs was not standardized, which may have influenced event detection. However, the performance of TWA was similar in the entire cohort and in the subgroup with implanted ICDs, suggesting that detection bias did not importantly influence our results.

Our study population consisted of patients who were referred for primary and secondary prevention of ventricular arrhythmias. Although risk stratification is more commonly applied to primary prevention patients in clinical practice, previous studies have confirmed that it is possible to identify low-risk patients within a cohort with previous documented sustained ventricular arrhythmias.[23] Left ventricular dysfunction is a major determinant of arrhythmia risk and the resultant survival benefit conferred by ICD placement, regardless of whether primary or secondary prevention patients are studied.[23,24] Accordingly, left ventricular dysfunction was an important selection criterion for this study, and

we did not exclude subjects who were referred for secondary prevention. Finally, although our study population consisted of patients who were referred for primary and secondary prevention of ventricular arrhythmias, the results in the primary prevention subgroup mirrored those of the entire study cohort. Thus, our data should be valid for the development of a new algorithm for prophylactic ICD placement.

Clinical Implications

The combined use of TWA, LVEF and PVS is a new approach to arrhythmia risk stratification that holds significant promise for targeting ICD therapy to those individuals who are most likely to benefit from this expensive intervention. Because it is difficult in practice to withhold ICD therapy from patients who are referred for secondary prevention even if low-risk characteristics can be identified, we propose a new strategy based on our data to guide patient selection for prophylactic ICD placement. Assessment of LVEF should be performed initially, and patients with LVEF $\leq$40% would have TWA testing. Patients with negative TWA results and LVEF 30%–40% would not undergo ICD placement because of the excellent prognosis in this subgroup. TWA+ patients would undergo ICD placement, and patients with either indeterminate TWA results or the combination of negative TWA results and LVEF $<$30% would have PVS to determine if ICD placement is indicated. Because nearly 65% of the patients in our study had either positive TWA test results or the combination of negative TWA results and LVEF30%–40%, this strategy would dramatically reduce the number of invasive PVS tests required, without compromising sensitivity. Furthermore, we identified a low-risk cohort with this approach that comprised 26% of the present study population. In the present study, patients with syncope who did not have previously documented arrhythmias and subjects who met MADIT-1 or MUSTT criteria were classified as primary prevention patients. It is recognized that the risk profile of our primary prevention patients may differ from that of MADIT-2 patients, who were not evaluated in the present study. Therefore, additional studies are required to determine if our proposed strategy is applicable to MADIT-2 patients.

The results of this study suggest that combined assessment of TWA, LVEF, and PVS could be used to identify low-risk patients with ischemic heart disease and severe left ventricular dysfunction who may not require ICD placement. In addition, our data support the use of TWA to guide therapy in subjects with less severe left ventricular dysfunction who were not addressed by the MADIT-2 trial.

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