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Influence of QRS Duration on the Prognostic Value of T Wave Alternans

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T Wave Alternans and QRS Duration. ***Introduction:*** **T wave alternans (TWA) is a promising new noninvasive marker of arrhythmia vulnerability that quantifies beat-to-beat changes in ventricular repolarization. Secondary repolarization abnormalities are common in subjects with wide QRS complexes. However, the relationship between TWA and QRS prolongation has not been evaluated. The goal of this study was to determine if QRS prolongation influences the prevalence or prognostic value of TWA.**

Methods and Results: **The study consisted of 108 consecutive patients with coronary artery disease and left ventricular ejection fraction ≤40% who were referred for electrophysiologic studies. Patients underwent TWA testing using bicycle ergometry in the absence of beta-blockers or antiarrhythmic drugs. The primary endpoint was the combined incidence of death, sustained ventricular arrhythmias, and appropriate implantable cardioverter defibrillator therapy. The prognostic value of TWA was assessed in the entire cohort and in two subgroups: QRS < 120 msec (normal, n = 62) and QRS ≥ 120 msec (prolonged, n = 46). TWA (hazard ratio 2.2, P = 0.03) and QRS prolongation (hazard ratio 2.2, P = 0.01) were both significant and independent predictors of arrhythmic events. QRS prolongation had no effect on the prevalence of positive TWA tests (QRS < 120 msec: 48%, QRS ≥ 120 msec: 50%, P = NS). TWA was a highly significant predictor of events in patients with a normal QRS (hazard ratio 5.8, P = 0.02). In contrast, TWA was not useful for risk stratification in subjects with QRS prolongation (hazard ratio 1.1, P = 0.8).**

Conclusion: **TWA is useful only for risk stratification in the absence of QRS prolongation. The presence of QRS prolongation and left ventricular ejection fraction ≤40% may be sufficient evidence of an adverse prognosis that additional risk stratification is not useful or necessary.** *(J Cardiovasc Electrophysiol, Vol. 13, pp. 770-775, August 2002)*

T wave alternans, QRS prolongation, left ventricular ejection fraction

Introduction

Abnormalities in ventricular repolarization contribute importantly to the pathogenesis of life-threatening ventricular arrhythmias among patients with coronary artery disease and left ventricular dysfunction.[1] The T wave is the surface ECG representation of the ventricular repolarization process. Visible alternation in the amplitude of the T wave (T wave alternans [TWA]) is a rare but significant finding that has been associated with malignant ventricular arrhythmias.[2,3] A method has been developed to detect more subtle microvolt levels of TWA.[4,5] Microvolt TWA subsequently was shown to be associated with inducible ventricular arrhythmias during electrophysiologic studies (EPS) as well as spontaneous arrhythmic events.[5-8] It is well recognized that the repolarization process can be affected by abnormal myocardial activation patterns. For example, persistent T wave changes can be observed after cessation of ventricular pacing, and similar findings have been described after radiofrequency ablation of manifest accessory pathways.[9] In addition, the presence of a prolonged QRS complex has been associated with an adverse prognosis.[10-13] However, the relationship between TWA and QRS prolongation has not been evaluated. We hypothesized that QRS prolongation may influence the prevalence of positive TWA tests and the prognostic value of TWA for arrhythmic events. Accordingly, we examined this question using a high-risk cohort of subjects with ischemic heart disease and left ventricular dysfunction that were referred for EPS.

Methods

Patients

This single-center study consisted of 108 consecutive patients at the University of Maryland Medical Center who were recruited over the 3-year period from 1997 to 2000. 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 (asymptomatic nonsustained ventricular tachy-

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cardia, syncope, sustained ventricular tachycardia, or ventricular fibrillation arrest). The exclusion criteria were atrial fibrillation, current use of Vaughn-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, and the study was approved by the institutional review board.

Twelve-Lead ECG

A 12-lead ECG was obtained in all patients before TWA testing (MAC-PC, Marquette Electronics Inc., Milwaukee WI, USA). QRS duration was measured automatically from the median beat using the Marquette 12 SL™ ECG analysis program and was dichotomized a priori using the standard cutpoint of 120 msec.[10,14] QRS ≥120 msec was considered prolonged, and QRS <120 msec was classified as normal.

T Wave Alternans

TWA testing was conducted before EPS using bicycle exercise to achieve a heart rate of 105 to 110 beats/min. Beta-adrenergic blockers were withheld for at least 24 hours before the study to reduce the risk of an inadequate heart rate response to exercise and because these agents reduce TWA independent of their effects on heart rate.[15,16] 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.[7] 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.[5]

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.[7] A total of 144 patients underwent TWA testing in this study. Patients with indeterminate TWA test results were excluded from the analysis of the effects of QRS prolongation on TWA (n = 36), yielding the 108 subjects that are the focus of this report. TWA tests were indeterminate because of excessive ectopy in 47% of cases and because of an inadequate heart rate response in 53%. Additional analyses were conducted to determine the effects of using a heart rate threshold ≥80 beats/min instead of ≥105 beats/min to define a complete TWA test ("B rules").[17] To qualify as a complete TWA test according to the "B rules," at least 1 minute of artifact-free data must be present without significant TWA within 5 beats/min of the maximal heart rate achieved.[17] Data were analyzed by two experienced readers who were blinded with respect to the clinical data and the results of EPS.

Electrophysiologic Testing

EPS was performed with the patients in the mildly sedated, postabsorptive state, as previously described.[18] 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.[19] Implantable cardioverter defibrillators (ICDs) were placed if patients had a positive EPS 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, 86 patients 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 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 predictive value of TWA for arrhythmic events was compared for subjects with QRS ≥120 msec (n = 62) and QRS <120 msec (n = 46). This is a secondary analysis of a prospective study that was initiated to evaluate the prognostic value of TWA in subjects with ischemic cardiomyopathy.

A Cox proportional hazards model was constructed to identify variables that were significantly associated with endpoint events. All variables that were 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: TWA, QRS ≥120 msec, 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

The patients in the study population had a mean age of 64 ± 10 years and a mean left ventricular ejection fraction of 28% ± 7%. All patients had significant coronary artery

TABLE 1
Clinical Characteristics of the Study Population

	QRS <120 msec (n = 62)	QRS ≥120 msec (n = 46)
Age (years)	63 ± 11	65 ± 9
Male (%)	77	83
Race (%)		
Caucasian	77	89
African-American	23	11
Left ventricular ejection fraction (%)*	29 ± 7	25 ± 7
Coronary artery bypass grafting (%)	38	52
New York Heart Association class (%)		
I	10	11
II	66	56
III	24	33
Prior sustained ventricular arrhythmias (%)	44	41
Inducible ventricular arrhythmias (%)	68	74
T wave alternans positive (%)	48	50
Implantable cardioverter defibrillator (%)	76	85
Cardiovascular medications (%)		
Aspirin	74	72
ACE inhibitor or ARB	81	80
Beta-blockers	73	76
Digoxin	56	52
Loop diuretic	65	63
Statin	55	57

*P = 0.003 for comparison of the two groups.
ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker.

disease by study design, and 44% had previously undergone coronary bypass surgery. The majority of patients had symptomatic New York Heart Association class II or III heart failure (90%). EPS was performed for primary prevention purposes in 57% of patients (nonsustained ventricular tachycardia 34%, syncope 23%) and to evaluate sustained ventricular tachycardia (34%) or ventricular fibrillation arrest (9%) in the remainder. A prolonged QRS (≥120 msec) was present in 46 subjects (43%). The conduction disturbance was a left bundle branch block in 19 cases, right bundle branch block in 5, and nonspecific intraventricular conduction delay in 22. When subjects with QRS ≥120 msec and QRS <120 msec were compared, prolonged QRS duration was associated with worse left ventricular function (25% ± 7% vs 29% ± 7%, P = 0.003). However, there were no significant differences between the two subgroups with respect to any other clinical variables, including age, race, New York Heart Association class, history of sustained ventricular arrhythmias, coronary bypass grafting, or cardiovascular medication use (Table 1).

Results of TWA and EPS Testing

Of the 144 subjects who underwent TWA testing, TWA was positive in 49% of patients, negative in 26%, and indeterminate in 25%. There were no complications from withholding beta-blockers before TWA testing. EPS testing was positive in 70% of patients. Sustained monomorphic ventricular tachycardia was the induced arrhythmia in 97% of EPS+ patients. ICDs were subsequently placed in 80% of the patients. As expected, patients with previously documented sustained ventricular arrhythmias were more likely to have a positive EPS (odds ratio 3.8 [1.5–9.7], P = 0.006). TWA (odds ratio 3.0 [1.3–7.0], P = 0.01), and Caucasian race (odds ratio 3.4 [1.2–9.4], P = 0.02) were significant predictors of EPS results. Patients with normal and prolonged QRS duration did not differ significantly with respect to TWA results, EPS results, or ICD use (Table 1).

Predictors of Endpoint Events

Mean duration of follow-up was 541 ± 396 days. A total of 40 arrhythmic events occurred during follow-up (37% of patients), including 11 deaths and 29 episodes of ventricular tachycardia treated with antitachycardia pacing (n = 10) or shocks (n = 19). TWA was a significant predictor of endpoint events (event rates: TWA+, 44%; TWA−, 24%; hazard ratio 2.2 [1.1–4.7], P = 0.03). Patients with indeterminate TWA results had an intermediate prognosis (28% event rate). When a cutoff ≥80 beats/min was used to define a complete TWA test ("B rules"), 11 patients were reclassified as TWA− instead of indeterminate, and the prognostic value of TWA was diminished (hazard ratio 1.7 [0.9–3.2], P = 0.10). QRS prolongation was the only other significant predictor of endpoint events (event rates: QRS ≥120 msec, 50%; QRS <120 msec, 27%; hazard ratio 2.2 [1.2–4.2], P = 0.01). Prolonged QRS duration remained a significant predictor of arrhythmic events after adjustment for left ventricular ejection fraction. There was a nonsignificant trend for EPS to be associated with endpoint events (event rates: EPS+, 42%; EPS−, 25%; hazard ratio 1.8 [0.8–3.9], P = 0.14). The indication for EPS was not a predictor of endpoint events (event rates: 35% in subjects with previous documented sustained ventricular arrhythmias, 39% in subjects referred for syncope or nonsustained ventricular tachycardia, P > 0.6). Both TWA and QRS prolongation remained significant predictors of events after adjustment for the EPS indication (primary vs secondary prevention). In multivariate analyses, TWA and QRS prolongation were the only independent predictors of events. The Kaplan-Meier curves of event-free survival for TWA and QRS prolongation are shown in Figure 1. The diagnostic characteristics of TWA, QRS prolongation, and EPS are listed in Table 2. QRS prolongation had lower sensitivity, higher specificity, and higher positive predictive value than TWA. EPS had lower specificity than TWA, but the sensitivities of the tests were similar.

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 13%, sotalol 3%). Importantly, there was no significant difference in the incidence of endpoint events when patients who were and patients who were not treated with antiarrhythmic drugs were compared (41% vs 36%, respectively; P = 0.7).

Influence of QRS Duration on TWA Risk Predictions

To characterize the influence of QRS duration on TWA risk predictions, the prognostic value of TWA was assessed separately in subjects with QRS ≥120 msec (n = 46) and QRS <120 msec (n = 62). TWA was a significant predictor of arrhythmic events in subjects with QRS <120 msec (event rates: TWA+, 38%; TWA−, 9%; hazard ratio 5.8 [1.3–25.3], P = 0.02; Fig. 2A). In contrast, TWA had no prognostic value for subjects with QRS ≥120 msec (event rates: TWA+, 52%; TWA−, 47%; hazard ratio 1.1 [0.5–2.7], P = 0.8; Fig. 2B). EPS also tended to be a better predictor of events in subjects with QRS <120 msec (haz-

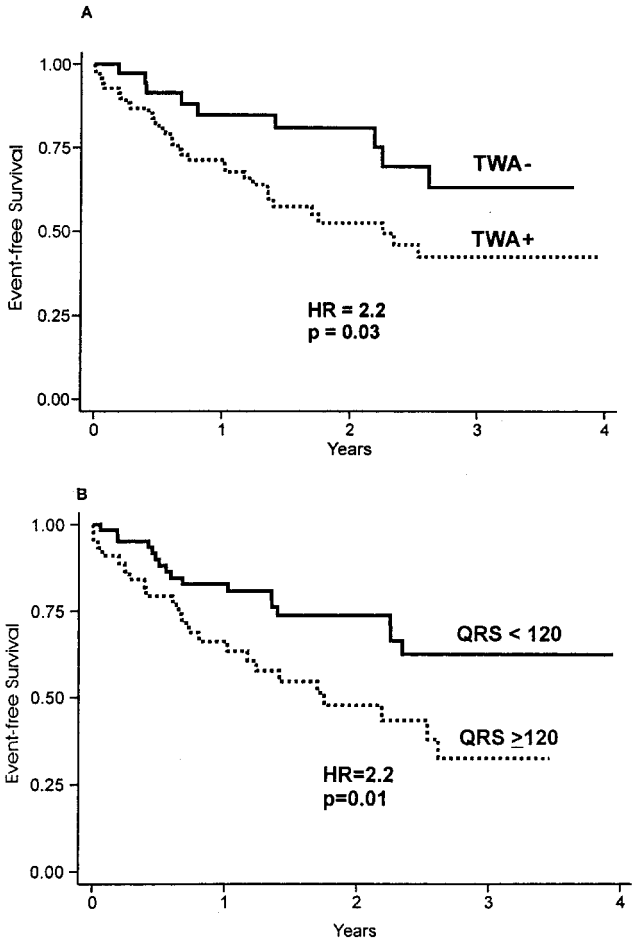

Figure 1. *Risk stratification for arrhythmic events. Kaplan-Meier curves of event-free survival are shown. (A) T wave alternans (TWA). (B) QRS duration.*

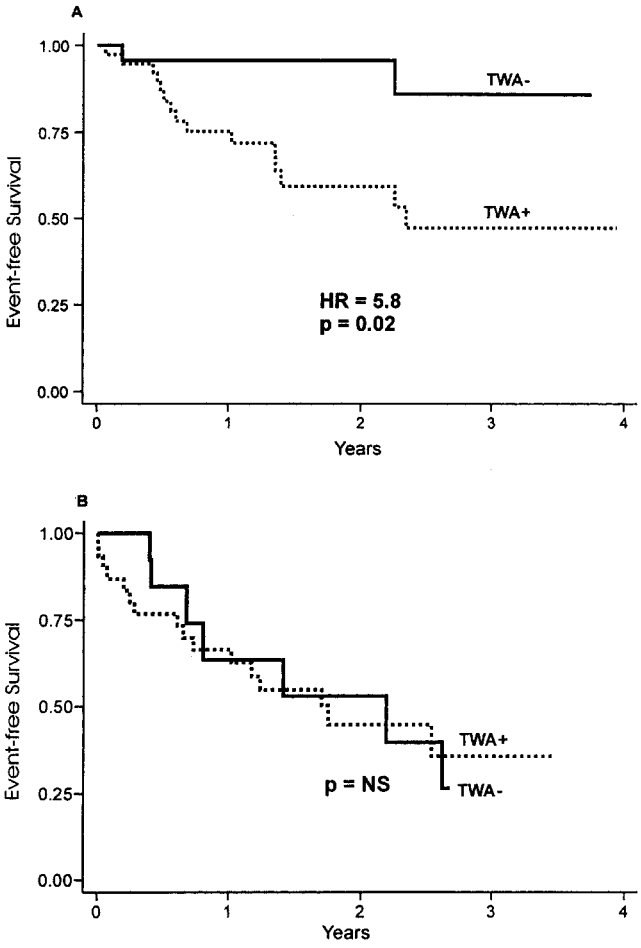

Figure 2. *Influence of QRS duration on the prognostic value of T wave alternans (TWA) for spontaneous arrhythmic events. Kaplan-Meier curves of event-free survival are shown. (A) QRS <120 msec. (B) QRS ≥120 msec.*

ard ratio 2.6 [0.8–9.2], P = 0.12) than in subjects with QRS ≥120 msec (hazard ratio 1.0 [0.4–2.8], P = 1.0).

Discussion

The major findings of this study are that QRS prolongation affects the prognosis but not the prevalence of TWA. TWA was a highly significant predictor of spontaneous arrhythmic events in subjects with a normal QRS duration. In contrast, TWA had no prognostic value for subjects with QRS prolongation.

Comparison with Previous Studies of TWA

To our knowledge, the present study is the first to examine specifically the impact of QRS duration on TWA risk predictions. Because TWA did not predict endpoint events in subjects with QRS prolongation, it is likely that the prognostic value of TWA in previous reports was importantly influenced by the composition of the populations that were studied. Many previous studies of TWA enrolled all patients who were referred for EPS, including subjects without structural heart disease.[5-7] QRS prolongation was either an exclusion criterion for these studies[8] or was infrequently observed.[5-7] As a result, the prognostic value of the TWA test was exaggerated. In contrast, TWA did not predict mortality in a low-risk cohort of postinfarction patients,[16] possibly because testing was performed during the acute phase of myocardial infarction, beta-blockers were not

TABLE 2
Event-free Survival Stratified by TWA, QRS, and EPS Test Results (n = 108)

	HR (95% CI)	Log Rank P Value	Sensitivity	Specificity	PPV	NPV
TWA	2.2 (1.1-4.7)	0.03	78%	43%	44%	76%
QRS ≥120 msec	2.2 (1.2-4.2)	0.01	58%	66%	50%	73%
EPS	1.8 (0.8-3.9)	0.14	80%	35%	42%	75%

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

withheld before testing,[15] or because the low incidence of events in this study precluded effective risk stratification. 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 left ventricular ejection fractions (27% vs 39%), and more arrhythmic events (35% vs 9%) than the patients in the multicenter study of Gold et al.[7] QRS prolongation is more common in subjects with advanced structural heart disease, and the high prevalence of this abnormality in our patient population (43% of patients) is consistent with other studies.[14] Because TWA had no prognostic value in subjects with QRS prolongation, it is not surprising that TWA was a less accurate predictor of arrhythmias in our study population than in previous reports (Fig. 1A).[5-8]

There are several potential mechanisms for the effects of QRS duration on TWA. The presence of disordered myocardial activation is a recognized precipitant of repolarization abnormalities.[9] However, QRS prolongation was not associated with an increased prevalence of positive TWA tests, suggesting that the poor performance of TWA in this cohort is not attributable to a nonspecific increase in TWA. Given these findings, changing the classification scheme for TWA (e.g., different voltage threshold, onset heart rate) is unlikely to improve its prognostic value in subjects with QRS prolongation. Rather, the poor performance of TWA in this patient subgroup may simply reflect the difficulty of performing additional risk stratification in patients who already have been characterized as high risk by the presence of QRS prolongation.[10-14] This hypothesis is supported by our observation that EPS tended to perform better in the absence of QRS prolongation. Conversely, our data suggest that patients with left ventricular ejection fraction $\leq$40% and QRS $<$120 msec represent an intermediate-risk cohort that is effectively risk stratified using TWA. Patients with QRS $<$120 msec and a negative TWA test had a very low event rate (Fig. 2A), suggesting that ICD placement may not be needed in this subgroup. Although combined analysis of TWA and the signal-averaged ECG may enhance risk stratification of subjects with normal QRS durations,[7,8] this strategy is not applicable to patients with QRS prolongation.[14]

Patients with indeterminate TWA results were excluded from most previous studies of TWA.[5-8] In the present study, patients with indeterminate 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.[19,20] Our data do not support the use of the "B rules" to decrease the prevalence of indeterminate TWA tests, because the prognostic value of TWA was diminished when these criteria were applied. In contrast, Klingenheben et al.[17] reported a low incidence of arrhythmic events among patients who were classified as TWA− using the "B rules." This discrepancy is likely attributable to the lower event rate and shorter duration of follow-up of the prior study.[17] The high prevalence of indeterminate TWA results in our cohort (25% of patients) is consistent with prior reports,[7,8,17] 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.[19,20] 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, congestive heart failure, Caucasian race).[21] Moreover, our subjects with nonsustained ventricular tachycardia were almost exclusively identified by telemetry during a hospitalization, which has been correlated with a higher inducibility rate.[22] 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.[15]

Prognostic Significance of QRS Prolongation

In the present study, subjects with QRS prolongation also had an increased incidence of arrhythmic events (Fig. 1B), which is in accordance with previous reports.[10-14] The prognostic value of QRS prolongation has been repeatedly demonstrated in subjects with many different forms of heart disease.[10-14] In the MADIT-1 study, the survival benefit conferred by prophylactic ICD placement was greater among subjects with a prolonged QRS, suggesting that this factor is specifically associated with an increased risk for arrhythmias.[10] QRS prolongation is indicative of slow and disordered impulse conduction, which is a recognized substrate for reentrant ventricular arrhythmias.[14] Moreover, the presence of left bundle branch block introduces contractile inefficiency and dyssynchrony, causing further progression of left ventricular dysfunction and worsening heart failure symptoms.[23,24] Cardiac resynchronization therapy has been demonstrated to improve exercise capacity in subjects with congestive heart failure and left bundle branch block,[25] and there is some evidence that this intervention reduces the risk for ventricular arrhythmias as well.[26] However, our study was not powered to determine if specific conduction defects (e.g., left bundle branch block vs right bundle branch block) have a more adverse prognosis or a greater influence on the prognostic value of TWA.

Study Limitations

The composite endpoint for this study is subject to some limitations. Although it is possible that some of the deaths may not have been due to ventricular arrhythmias, all-cause mortality was used because of the difficulties inherent in determining cause-specific mortality in clinical trials.[27] 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 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 should be confirmed in subjects with

nonischemic dilated cardiomyopathy or other forms of structural heart disease.

Conclusion

The results of this study suggest that TWA is only useful for risk stratification in the absence of QRS prolongation. The presence of QRS prolongation and left ventricular ejection fraction ≤40% may be sufficient evidence of an adverse prognosis that additional risk stratification is not useful or necessary.

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