Prognostic Value and Temporal Behavior of the Planar QRS-T Angle in Patients With Nonischemic Cardiomyopathy

Behzad B. Pavri, MD; Matthew B. Hillis, MD; Haris Subačius, MA; Genevieve E. Brumberg, MD; Andi Schaechter, BSN, RN; Joseph H. Levine, MD; Alan Kadish, MD; for the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators

Background—The planar QRS-T angle can be easily obtained from standard 12-lead ECGs, but its predictive ability is not established. We sought to determine the predictive ability of the planar QRS-T angle in patients with nonischemic cardiomyopathy and to assess QRS-T angle behavior over time.

Methods and Results—Baseline QRS-T angles from 455 patients in the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial were measured. All patients had nonischemic cardiomyopathy, New York Heart Association class I to III heart failure, and nonsustained ventricular tachycardia or frequent ventricular ectopy. The primary end point (a composite of total mortality, appropriate implantable cardioverter-defibrillator shock, or resuscitated cardiac arrest) occurred in 25 of 172 patients (14.5%) with a QRS-T angle $\geq 90^\circ$ and in 72 of 283 patients (25.4%) with a QRS-T angle $>90^\circ$ (hazard ratio, 1.93; 95% confidence interval, 1.23 to 3.05; $P=0.002$). A QRS-T angle $>90^\circ$ remained a significant predictor of the primary end point ($P=0.039$) after adjustment for treatment group, age, gender, QRS duration, left bundle-branch block, left ventricular ejection fraction, New York Heart Association class III, atrial fibrillation, and diabetes mellitus. The secondary end point (total mortality) occurred in 17 of the 172 patients (9.9%) with a QRS-T angle $\geq 90^\circ$ and in 49 of the 283 patients (17.3%) with a QRS-T angle $>90^\circ$ (hazard ratio, 1.79; 95% confidence interval, 1.03 to 3.10; $P=0.016$). A sample of 152 patients with multiple follow-up ECGs was analyzed to assess temporal QRS-T angle behavior. Changes in the QRS-T angle correlated with changes in left ventricular ejection fraction and QRS duration over time ($P<0.001$).

Conclusions—A planar QRS-T angle $>90^\circ$ is a significant predictor of a composite end point of death, appropriate implantable cardioverter-defibrillator shock, or resuscitated cardiac arrest in nonpaced, mild to moderately symptomatic patients with nonischemic cardiomyopathy with frequent or complex ventricular ectopy. QRS-T angles changed predictably with left ventricular ejection fraction and QRS duration. (Circulation. 2008;117:3181-3186.)

Key Words: cardiomyopathy ■ electrocardiography ■ heart failure ■ prognosis

Patients with ischemic and nonischemic cardiomyopathy are at increased risk for sudden cardiac death, and implantable cardioverter-defibrillators (ICDs) reduce this risk.1–3 Clinical and ECG parameters such as nonsustained ventricular tachycardia, QRS prolongation, left bundle-branch block (LBBB), and the heart rate–adjusted QT interval have been shown to be predictive of cardiovascular events in certain populations.4–6 However, the prognostic role of these and other parameters in patients with nonischemic cardiomyopathy has not been well established. Based in large part on available clinical trial data, the left ventricular ejection fraction (LVEF) has been relied on heavily to determine which patients are at high risk of sudden cardiac death and therefore would benefit most from ICD implantation for the primary prevention of sudden cardiac death. Because the LVEF is neither highly specific nor highly sensitive as a risk factor for sudden cardiac death, considerable interest exists in identifying novel risk factors that may be more useful than, or adjunctive to, those currently employed. Ideally, a clinically useful risk factor would not only be sensitive and specific but obtained easily at minimal risk and cost to the patient.

Clinical Perspective p 3186

The difference between QRS and T-wave vectors in 3-dimensional space, the spatial QRS-T angle, has been shown to predict cardiovascular events and mortality in several different patient populations. An abnormal spatial QRS-T angle is a strong and independent predictor of...
cardiovascular mortality in general populations and in patients with acute ischemic chest pain.\textsuperscript{7–10} Similarly, it has been shown to predict arrhythmic death in patients who have had myocardial infarctions and to predict cardiovascular events in women with suspected myocardial ischemia.\textsuperscript{11,12} The calculation of the spatial QRS-T angle requires dedicated software that is not widely available and cannot be derived by visual ECG analysis after acquisition. In contrast, the planar QRS-T angle is obtained easily from a standard 12-lead ECG by visual examination but has not been well established to have prognostic ability.

The Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial was a prospective, randomized, multicenter trial of ICD therapy in patients with nonischemic cardiomyopathy.\textsuperscript{2} In this population, ICD therapy resulted in a significant reduction in sudden cardiac death and a trend toward decreased all-cause mortality. We sought to determine whether the planar QRS-T angle calculated from standard 12-lead ECGs was predictive of adverse events in the DEFINITE population. Furthermore, we attempted to assess the stability of the QRS-T angle over time and correlate changes in QRS-T angle with changes in established cardiovascular risk factors (New York Heart Association [NYHA] class, LVEF, and QRS duration) over the course of the trial.

Methods
Baseline ECG Analysis
The present study is a post hoc analysis of the DEFINITE trial, which randomized 458 patients with nonischemic dilated cardiomyopathy to standard medical therapy or standard medical therapy plus an ICD.\textsuperscript{2} Inclusion criteria were age between 21 and 80 years, nonischemic cardiomyopathy with a LVEF \( \leq \) 35\%, history of symptomatic heart failure, and the presence of 1 of the following within the past 6 months: nonsustained ventricular tachycardia on telemetry monitoring or Holter monitoring and/or an average of 10 premature ventricular complexes per hour on a 24-hour Holter monitor. Patients were excluded from enrollment if they had NYHA class IV heart failure, were candidates for an ICD, or had a permanent pacemaker. The primary end point of DEFINITE was death due to any cause. A prespecified secondary end point was sudden death due to an arrhythmia. At least 85\% of patients received \( \beta\)-blockers, angioten-
sin-converting enzyme inhibitors, and diuretics. The ICDs were programmed to VVI pacing at 40 bpm with a single tachycardia detection window programmed to a lower rate of 180 to 200 bpm. Antitachycardia pacing was not programmed unless monomorphic ventricular tachycardia was induced at a rate of 140 to 190 bpm. The cause of death was determined by an events committee whose members were unaware of the patients’ treatment assignments.

Baseline ECGs were available for 455 of the 458 patients enrolled in the DEFINITE trial. Measurements of the frontal QRS and T wave axes were made and used to calculate the baseline planar QRS-T angle. The planar QRS-T angle was defined as the angle between the maximum QRS and T wave vectors in the frontal plane. All ECGs were analyzed by 2 authors (M.B.H. and G.E.B.) who were blinded to outcomes. A third blinded author (B.B.P.) was used to adjudicate any disagreements in the measured QRS-T angle (most often due to difficulty in T-wave axis interpretation).

End Points
The primary end point was defined as a composite of death, appropriate ICD shock (in the group randomized to ICD), or resuscitated cardiac arrest (in the group not randomized to ICD). Total mortality alone was used as the secondary end point, in part because a previous analysis of the DEFINITE trial showed that appropriate ICD shocks were not a reliable surrogate for sudden cardiac death.\textsuperscript{13} A receiver operating characteristic curve analysis of the baseline QRS-T angle suggested that a cutoff of 90\(^{\circ}\) corresponded to the optimal trade-off between sensitivity and specificity for predicting the primary end point. To evaluate bias for the 90\(^{\circ}\) cut point, we performed bootstrap analysis with 1000 random samples drawn with replacement from the original sample. The bootstrapping analysis provided additional support for the use of 90\(^{\circ}\) as a cutoff value for the QRS-T angle as the predictor of the primary end point. This exact value (90\(^{\circ}\)) was the mode among the bootstrap samples, and cutoff values in close proximity to 90\(^{\circ}\) accounted for nearly one half of the results. We therefore sought to determine the prognostic importance of a baseline planar QRS-T angle >90\(^{\circ}\) in patients enrolled in the DEFINITE trial.

QRS-T Angle Behavior Over Time
To assess QRS-T angle behavior over time, we separately analyzed all available ECGs (baseline and all follow-up) from 100 randomly selected patients. In addition, ECGs from an additional 66 patients who had \( \geq 3 \) follow-up tracings were analyzed. QRS-T angle changes related to the development or resolution of bundle-branch block or intraventricular conduction delay, pacing, or the development of uninterpretable T-wave axis (due to macrovolt T-wave alternans, frequent premature ventricular complexes, or an indeterminate T-wave axis) were excluded from this temporal analysis, given the known effect of such changes on the T-wave axis.\textsuperscript{14–19} With these exclusions, the investigation of QRS-T angle behavior over time was performed on a sample of 152 patients.

Statistical Analysis
Baseline patient characteristics in the 2 groups were compared with \( t \) tests and \( \chi^2 \) tests as appropriate for the measurement level of the variables. The Kaplan–Meier methodology was used to plot survival curves for primary and secondary end points. The Tarone-Ware test was performed to assess the effects of QRS-T angle >90\(^{\circ}\) as a predictor of the end points.\textsuperscript{20} The Tarone-Ware test was employed (instead of the log-rank test) to adjust for the relative scarcity of data toward the end of the trial and because predictive value of the QRS-T angle would be expected to diminish as time from measurement to event increased. A Cox proportional hazards model was used to estimate the hazard ratios (HRs) and 95\% confidence intervals, assess the performance of the QRS-T angle in a multivariable model, and verify the proportional hazards assumption.\textsuperscript{21} The following variables were studied: treatment group (standard medical therapy alone versus standard medical therapy plus ICD), age, gender, QRS duration, LBBB, LVEF, NYHA class III, history of atrial fibrillation, and diabetes mellitus. A likelihood ratio test was used to assess associations. The reference model was the model with all the covariates, and the more complex nested model was the one with QRS-T angle added to the set of covariates. Because the QRS-T angle is a composite of the frontal plane QRS and T-wave axes, these axes were also individually assessed as single predictors with the use of parallel Cox models. SPSS software (version 15) was used to perform the analyses.

Random intercepts-and-slopes models (SAS Proc mixed) were used to estimate the relationships between QRS-T angles and clinically established time-varying covariates (LVEF, QRS duration, and NYHA class) during follow-up, as well as to estimate the intraclass correlation coefficient. Pearson correlation coefficients between baseline, first-year, and second-year QRS-T angles were used to estimate test-retest reliability.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
ECG Analysis
Four hundred twenty-five (93\%) of the 455 baseline ECGs were easily interpretable, and 30 (7\%) required adjudication
before a QRS-T angle was determined. Four hundred nine (89.9%) of the 455 ECGs were initially analyzed by computer at the enrolling center, and the ECG readers agreed with the computer-generated QRS and T axes in 396 (96.8%) of these 409 computer-analyzed ECGs. Two ECGs (0.4%) were found to have an indeterminate T-wave axis. Because it has been shown previously that an indeterminate T-wave axis is abnormal and associated with an adverse prognosis, the 2 patients with indeterminate T-wave axes were included in the group in which QRS-T measurements were >90°.22

Patient Characteristics

The baseline patient characteristics are summarized in Table 1. Two hundred eighty-three patients (62.2%) had a QRS-T angle >90°, and 172 patients (37.8%) had a QRS-T angle ≤90°. Patients with QRS-T angles >90° were more likely to be older (59.9±12.5 versus 55.4±13.2 years) and have greater QRS duration (119.8±30.1 versus 107.2±24.5 ms), lower ejection fraction (20.6±5.8% versus 22.6±6.1%), leftward QRS axis (−15.9±49.3° versus 19.0±43.5°), LBBB (25.8% versus 9.9%), or history of atrial fibrillation (27.9% versus 19.2%) compared with patients who had QRS-T angles ≤90°. No significant differences were found among the other characteristics studied between the 2 groups.

Outcomes

During a mean follow-up of 29.7±14.5 months in the DEFINITE trial, the primary end point of death, appropriate ICD shock, or resuscitated cardiac arrest occurred in 72 of the 283 patients (25.4%) with a QRS-T angle >90° and in 25 of the 172 patients (14.5%) with a QRS-T angle ≤90° (HR, 1.95; 95% confidence interval, 1.24 to 3.08; P=0.002), as shown in Table 2. Kaplan–Meier survival curves for freedom from the primary end point are shown in the Figure, and individual event rates classified by QRS-T angle category are shown in Table 3. The secondary end point of total mortality occurred in 49 of the 283 patients (17.3%) with a QRS-T angle >90° and in 17 of the 172 patients (9.9%) with a QRS-T angle ≤90° (HR, 1.81; 95% confidence interval, 1.04 to 3.13; P=0.016), as shown in Table 2.

Used as a continuous variable, QRS-T angle was a significant predictor of the primary end point (HR, 1.05 for each
follow-up were used to estimate test-retest reliability over angle measurements from baseline and first- and second-year Pearson correlation coefficients between pairs of QRS-T

Figure. Kaplan–Meier estimates of freedom from primary end point among patients with QRS-T angles ≤90° and >90°.

Multivariable analysis demonstrated that after adjustment for treatment group (standard medical therapy alone versus standard medical therapy plus ICD), age, gender, QRS duration, LBBB, LVEF, NYHA class III, history of atrial fibrillation, and diabetes mellitus, a QRS-T angle >90° remained a statistically significant predictor of the primary end point (P=0.039 for likelihood ratio test). These covariates were chosen on the basis of their established clinical utility. In the multivariable model, NYHA class III rating was the only statistically significant predictor of outcome in addition to QRS-T angle (P=0.003). A trend was registered for QRS duration (HR, 1.008; P=0.087), suggesting that the primary end point tended to occur more frequently in patients with a wider QRS complex.

The effect of QRS-T angle on the secondary end point was not statistically significant in the multivariable model (P=0.263 for likelihood ratio test). Because of the smaller number of events and to avoid “overfitting,” treatment assignment and gender were not controlled in the multivariable model for the secondary end point. NYHA class III rating (P=0.022) and history of atrial fibrillation (P=0.038) were predictors of death in the multivariable model after controlling for the other covariates, with an additional trend for diabetes mellitus (P=0.07).

Table 3. Individual Events by QRS-T Angle Classification*

<table>
<thead>
<tr>
<th>QRS-T Angle Class</th>
<th>Death</th>
<th>Resuscitated Cardiac Arrest</th>
<th>Appropriate Shock</th>
<th>Primary End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤90°</td>
<td>17</td>
<td>1</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>&gt;90°</td>
<td>49</td>
<td>2</td>
<td>25</td>
<td>72</td>
</tr>
</tbody>
</table>

*The total number of patients experiencing the primary end point is less than the sum of individual events because some patients experienced >1 appropriate shock.

time. The correlation was 0.63 (n=80) between baseline and first-year measurements and 0.87 (n=61) between first- and second-year measurements (P<0.001 for both comparisons).

Changes in LVEF and QRS duration were associated with changes in QRS-T angle during follow-up. Specifically, in the LVEF range of 30% to 40%, for every 5% decrease in LVEF, the QRS-T angle widened by ≈5° (P<0.001). For every 10-ms increase in QRS duration, the QRS-T angle widened by ≈6±1.3° (mean±SE; P<0.001). An improvement in NYHA class from III/IV to class I was associated with a 17.5±8.7° (mean±SE) narrowing of the QRS-T angle, but this effect did not reach statistical significance (P=0.11). When ranked outcome data were used to adjust for the nonnormal distribution of QRS-T angles, the relationship between QRS-T angle and NYHA class changes during follow-up became statistically significant (P<0.001), reinforcing the trend-level finding reported above. Relationships with LVEF and QRS duration remained significant in this nonparametric analysis.

Discussion

To our knowledge, this is the first study to assess the ability of the planar QRS-T angle to predict adverse events in a population of patients with nonischemic cardiomyopathy. The present analysis demonstrates that a planar QRS-T angle >90° in the frontal plane is a significant predictor of adverse outcomes in these patients. A relative risk of 1.93 suggests that for patients in the DEFINITE trial, a planar QRS-T angle >90° was associated with a near doubling of the risk of death, appropriate ICD shock, or resuscitated cardiac arrest. The Kaplan–Meier curves begin to separate early (within the first year) and then continue to stay separate. A planar QRS-T angle >90° remained a predictor of the primary end point even when controlling for established risk factors such as age, gender, QRS duration, LBBB, LVEF, NYHA class III, and history of atrial fibrillation and diabetes mellitus by multivariable analysis.

Total mortality alone was also greater in patients with QRS-T angles >90° but failed to remain statistically significant when controlling for covariates, possibly related to a small absolute number of deaths. Total mortality was selected as a secondary end point because of the recently reported observation that appropriate shocks are not a surrogate for aborted sudden death episodes in the DEFINITE trial.13

A widening QRS-T angle likely represents a continuum of worsening underlying pathology and outcomes. A narrow planar QRS-T angle, <45°, has been described previously in normal patient populations.23–25 Conversely, planar QRS-T angles >45° to 60° have been described as abnormal and

**QRS-T Angle Behavior Over Time**

Pearson correlation coefficients between pairs of QRS-T angle measurements from baseline and first- and second-year follow-up were used to estimate test-retest reliability over

Image 59x509 to 287x726

3184 Circulation June 24, 2008
found in a small percentage of professional athletes, patients with hypertension, and patients with acute and remote myocardial infarctions. A wide QRS-T angle likely reflects the presence of abnormal depolarization and repolarization. Widened QRS-T angles are commonly associated with left ventricular hypertrophy, bundle-branch block, pacing, and ischemia, which are conditions known to be associated with abnormal electrical activation. Because all patients in the present analysis had nonischemic cardiomyopathy, the finding of widened QRS-T angles in the majority of these patients is not surprising. Receiver operating characteristic analysis suggested that a cut point of 90° provided optimal sensitivity and specificity for the primary end point in this already sick population.

This is also the first study to assess the behavior of the planar QRS-T angle over time in a large population. We found only 1 study that described planar QRS-T angle changes in 44 patients with treatment of hypertension, in which the QRS-T angle narrowed with improved blood pressure control and the duration of follow-up was not specified. In our study, the QRS-T angle correlations between baseline and year 1 and between years 1 and 2 showed significant temporal stability. However, the correlation between baseline and year 1 was not as strong as between years 1 and 2, which may have been due to medical stabilization as the trial progressed. The changes in QRS-T angle correlated with changes in LVEF, QRS duration, and NYHA class, fitting this novel measurement into a context of well-established cardiovascular risk factors. The importance of understanding the dynamic nature of new ECG risk markers was recently highlighted by the preliminary results of the Alternans Before Cardioverter Defibrillator (ABCD) markers was recently highlighted by the preliminary results of understanding the dynamic nature of new ECG risk markers was recently highlighted by the preliminary results of the Alternans Before Cardioverter Defibrillator (ABCD) trial, in which microvolt T-wave alternans testing was no longer predictive of outcomes after 12 months.

The present finding that a planar QRS-T angle >90° was predictive of adverse events is consistent with previous studies that found a wide spatial QRS-T angle to be a strong predictor of cardiovascular events in several different patient populations. It is of interest to note that a modest correlation between the planar QRS-T angle and the spatial QRS-T angle has been described among patient populations in whom both angles have been measured. The wide-spread clinical use of other ECG risk markers such as signal-averaged ECGs and microvolt T-wave alternans has been limited in part because of the necessity of specialized equipment. The ability to easily measure the planar QRS-T angle from a standard 12-lead ECG is therefore particularly attractive and could be incorporated into automated ECG risk scoring, as has been proposed recently.

Limitations

The present study is a post hoc analysis of the DEFINITE trial, which was not designed to evaluate the prognostic ability of an abnormal QRS-T angle. The present study did not have the power to detect moderate HR differences for secondary end points or to detect moderate associations between changes in QRS-T angle and other features during follow-up. The 90° cutoff is derived from patients enrolled in the DEFINITE trial and must be validated in future research. Although QRS-T angle changes over time were associated with changes in LVEF, QRS duration, and NYHA class, there may be other factors that affect the QRS-T angle, such as ischemia, electrolyte abnormalities, and blood pressure control, which were not studied in this analysis. The planar QRS-T angle may be more or less useful in other patient populations. Finally, it is possible that the spatial QRS-T angle may have provided better predictive accuracy had it been measured.

Conclusions

A planar QRS-T angle >90° in the frontal plane, as measured from a standard 12-lead ECG, was a significant and independent predictor of a composite end point of death, appropriate ICD shock, or resuscitated cardiac arrest in patients in the DEFINITE trial. The majority of ECGs in the present analysis had readily analyzable data, increasing the clinical applicability of this simple measurement. The QRS-T angle remains stable over the time periods analyzed, and when changes occur, they correlate with changes in other established clinical parameters. Prospective studies of the utility of the planar QRS-T angle for the prediction of sudden cardiac death and need for prophylactic defibrillator implantation in this and other patient populations are warranted.

Disclosures

None.

References

Clinical Perspective

Current recommendations for implantable cardioverter-defibrillator (ICD) implantation for primary prevention of sudden death are neither highly sensitive nor specific. Many patients with ICDs do not receive appropriate shocks, and the majority of patients who experience sudden death do not meet current criteria for ICD implantation. Additional criteria that improve sensitivity and specificity would be beneficial, especially if they were widely available at low cost. The QRS-T angle has been proven to be predictive of outcomes in various populations. We sought to determine the predictive ability of the planar QRS-T angle (the angle between the frontal QRS and T-wave axes) in 455 patients in the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial. The primary end point (a composite of total mortality, appropriate ICD shock, or resuscitated cardiac arrest) occurred nearly twice as often in patients with a QRS-T angle < 90° compared with patients with a QRS-T angle ≥ 90° (hazard ratio, 1.95; 95% confidence interval, 1.24 to 3.08; P = 0.002). A QRS-T angle > 90° remained a significant predictor of the primary end point (P = 0.039) after adjustment for treatment group, age, gender, QRS duration, left bundle-branch block, left ventricular ejection fraction, New York Heart Association class III, atrial fibrillation, and diabetes mellitus. The secondary end point (total mortality) also occurred more often in patients with a QRS-T angle < 90° compared with patients with a QRS-T angle ≥ 90° (hazard ratio, 1.81; 95% confidence interval, 1.04 to 3.13; P = 0.016). In the present analysis, a planar QRS-T angle > 90° was a significant predictor of a composite end point of death, appropriate ICD shock, or resuscitated cardiac arrest in cardiomyopathy patients selected for primary prevention ICDs. Future studies that incorporate QRS-T angle along with other clinical criteria may improve selection of ICD recipients.
Prognostic Value and Temporal Behavior of the Planar QRS-T Angle in Patients With Nonischemic Cardiomyopathy
Behzad B. Pavri, Matthew B. Hillis, Haris Subacius, Genevieve E. Brumberg, Andi Schaechter, Joseph H. Levine and Alan Kadish
for the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators

*Circulation.* 2008;117:3181-3186
doi: 10.1161/CIRCULATIONAHA.107.733451

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/117/25/3181

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation* is online at:
http://circ.ahajournals.org//subscriptions/