Predicting Ventricular Arrhythmias in Patients With Ischemic Heart Disease
Clinical Application of the ECG-Derived QRS-T Angle

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Background—In patients with primary prevention implantable cardioverter-defibrillators (ICDs), the incidence of life-threatening ventricular arrhythmias resulting in ICD therapy is relatively low, prompting for better risk stratification. The aim of this study was to assess the value of the QRS-T angle for prediction of ICD therapy and mortality in primary prevention patients with ischemic heart disease.

Methods and Results—ICD patients (n=412, 361 men; age, 63±11 years) with ischemic heart disease and a left ventricular ejection fraction ≤40% were included. After device implantation, the occurrence of appropriate ICD therapy and mortality was noted. A survival analysis was performed comparing patients with a planar QRS-T angle ≤90° (n=124, 30%) with patients with a planar QRS-T angle >90° before device implantation. Furthermore, patients with a spatial QRS-T angle ≤100° (n=56, 14%) were compared with patients with a spatial QRS-T angle >100° before implantation. For patients with a planar QRS-T angle >90° as compared with ≤90°, the adjusted hazard ratio for the occurrence of appropriate device therapy was 2.4 (95% CI, 1.1 to 5.2); a spatial QRS-T angle >100° was associated with an adjusted hazard ratio of 7.3 (95% CI, 1.0 to 53.8). Furthermore, a spatial QRS-T angle ≤100° exhibited a positive predictive value of 98% (95% CI, 95 to 100) for the prediction of an appropriate therapy-free follow-up.

Conclusions—A wide QRS-T angle is a strong predictor of appropriate device therapy in primary prevention ICD recipients with ischemic heart disease. Furthermore, a spatial QRS-T angle ≤100° might be of value in the identification of patients in whom, although currently indicated, ICD treatment should be reconsidered. (Circ Arrhythmia Electrophysiol. 2009;2:548-554.)

Key Words: implantable cardioverter-defibrillator • electrocardiography • ventricular arrhythmia • primary prevention • ischemic heart disease

Sudden cardiac death, mainly caused by ventricular arrhythmias, accounts for approximately 50% of all cardiac mortality worldwide.1–3 It is recognized that patients with ischemic heart disease and depressed left ventricular ejection fraction (LVEF) are at high risk of sudden cardiac death.4,5 and large randomized trials have demonstrated that implantable cardioverter-defibrillator (ICD) therapy reduces all-cause mortality, as well as sudden cardiac death.6–10 Implementation of these results in the international guidelines resulted in a significant increase of the number of ICD implantsations.11,12 However, long-term follow-up studies in currently indicated patients show a relatively low incidence of ventricular arrhythmias that trigger ICD therapy.13 Additionally, approximately 6% of ICD patients have severe device-related adverse events (ie, pocket infections, sepsis), causing the need for surgical reintervention, additional hospitalization, or even death.14,15 This led to critical appraisal of the widespread application of ICD therapy and stressed the need for more precise risk stratification criteria.16 In an attempt to identify those criteria, post hoc analyses of the second Multicenter Automatic Defibrillator Implantation Trial (MADIT II) revealed several clinical criteria associated with an increased risk for ventricular arrhythmias resulting in appropriate device therapy.17–19 Thus far, however, in patients with low LVEF, no criteria have been recognized that may identify patients at low risk of ventricular arrhythmias during follow-up. If possible to identify a low-risk population, ICD therapy in this group may be reconsidered.

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Recently, a wide angle between the QRS and T axes, the QRS-T angle, on the standard 12-lead ECG was recognized

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as a novel and easy applicable marker of increased risk for cardiovascular mortality.20,21 Subsequently, a wide QRS-T angle was found to be associated with the increased incidence of appropriate device therapy and mortality in primary prevention ICD recipients with nonischemic cardiomyopathy.22 However, no data are available on the value of the QRS-T angle in ICD patients with IHD.

The aim of the current study was to assess the value of the QRS-T angle in predicting life-threatening ventricular arrhythmias in primary prevention ICD patients with IHD. Furthermore, the value of the QRS-T angle was evaluated as a parameter to identify patients at low risk for ventricular arrhythmias.

Methods

Patients

Patients with IHD who underwent implantation of an ICD, based on the international treatment guidelines, in the Leiden University Medical Center were selected for the current study.11 Criterion for inclusion were a depressed LVEF (<40%) with or without a history of non-sustained ventricular tachycardia. Since 1996, these patients were prospectively registered in the departmental Cardiology Information System (EPD-Vision).23 Before implantation, a comprehensive assessment of patient characteristics was performed as described previously.24

During follow-up, the occurrence of appropriate ICD therapy and patient mortality was noted. In addition, for the purpose of this study, the ECG made before implantation was analyzed.

ICD Implantation and Follow-Up

All defibrillator systems were implanted transvenously without thoracotomy. Device follow-up was scheduled every 3 to 6 months. All printouts were carefully checked for appropriate and inappropriate ICD therapy. In the case of any ICD therapy, an electrophysiologist, blinded to QRS-T measurements, determined whether or not the ICD therapy was appropriate. All therapies, either antitachycardia pacing (ATP) or shock, were classified as appropriate when they occurred in response to life-threatening arrhythmias (ventricular tachycardia or ventricular fibrillation) and as inappropriate when triggered by sinus or supraventricular tachycardia, T-wave oversensing, or electrode dysfunction.

Defibrillators were programmed as follows: ventricular arrhythmia faster than 150 bpm was monitored by the device without consequent defibrillator therapy. Ventricular arrhythmias faster than 188 bpm were initially attempted to be terminated with 2 bursts of ATP and, after continuation of the arrhythmia, with defibrillator shocks. In the case of a ventricular arrhythmia faster than 210 bpm, device shocks were the initial therapy. Furthermore, atrial arrhythmia detection was set to >170 bpm with supraventricular tachycardia discriminators enabled. Settings were adapted only when clinically indicated (ie, hemodynamically well-tolerated ventricular tachycardia at high rate; ventricular tachycardia in the monitor zone).

ECG Analysis

First, the quality of ECGs was evaluated. If electrode displacement, missing leads, or signal noise was present, the ECGs were excluded from the analysis. Because right ventricular pacing alters normal cardiac conduction and results, by definition, in an abnormal QRS-T angle, patients with a pacemaker were excluded from the analysis.25

Subsequently, the ECGs were analyzed with a dedicated computer program (LEADS, Leiden ECG Analysis and Decomposition Software).26 Full details on the computation method and LEADS based values of vector characteristics in healthy subjects have been extensively described earlier.27 In short, the software converts the standard ECG into a vectorcardiogram and computes the 3D orientation of the QRS- and T-axes. Thereafter, the QRS-T angle is calculated in the plane formed by the QRS- and T-axes, the spatial QRS-T angle. In addition, the more commonly used but less precise projection of the spatial QRS-T angle in the frontal plane, the planar

QRS-T angle, was computed. Previous studies demonstrated that a spatial QRS-T angle wider than 100° is associated with the presence of cardiac disease and increased cardiovascular mortality.20,21 Pavri et al22 recently demonstrated that a planar QRS-T angle wider than 90° is associated with an increased incidence of appropriate device shocks and mortality. In the present study, these cutoffs (100° for the spatial and 90° for the planar QRS-T angle) were applied.

Statistical Analysis

A survival analysis comprising of the following end points was performed: (1) first appropriate ICD therapy (ATP and/or shock); (2) all-cause mortality; and (3) a composite end point of all-cause mortality and first appropriate device therapy, whichever occurred first. ICD recipients with a narrow QRS-T angle were compared with those with a wide QRS-T angle. The points of cutoff were predefined as described above, 100° for the spatial and 90° for the planar QRS-T angle. Cumulative event rates of end points were analyzed by the method of Kaplan–Meier. Relationships between baseline parameters and end points were assessed with Cox proportional hazard regression analysis. For the composite end point, survival time was defined as time to all-cause death or appropriate device therapy, whichever occurred first. For each variable, a hazard ratio (HR) with a 95% CI was calculated. Therapy-free follow-up was defined as a study follow-up without the occurrence of appropriate ICD therapy.

Continuous data are expressed as mean±SD or median and quartiles where appropriate; dichotomous data are presented as numbers and percentages. Comparison of data at baseline was performed with the Student t test for unpaired data and χ2 tests with Yates correction when appropriate.

Results

Patients and Follow-Up

A total of 460 patients with ischemic heart disease and a LVEF ≤40% underwent ICD implantation for primary prevention of sudden cardiac death in the Leiden University Medical Center. Thirty-two (7%) patients were excluded because of the presence of a pacemaker and 16 (3%) patients were excluded because their ECG before device implantation could not be analyzed because of technical reasons such as electrode displacement, missing leads, or signal noise. The remaining 412 (90%) ICD recipients (63±11 years, 88% men) were included in the analysis and were followed for 22±17 months (range, 0 to 77 months). Baseline characteristics are summarized in Table 1.

During follow-up, 46 (11%) patients died, and a total of 482 episodes of appropriate device therapy for ventricular arrhythmias occurred in 56 (14%) patients, 386 episodes of ventricular arrhythmia terminated by ATP in 35 (8%) patients, and 96 episodes triggering device shocks in 28 (7%) patients. During follow-up, the first end point (first appropriate device therapy) was reached in 56 patients (24 shock, 32 ATP), the second end point (all-cause death) was reached in 46 patients, and the composite end point (death or first appropriate device therapy) was reached in 96 patients (40 patients all-cause deaths, 56 appropriate therapy).

QRS-T Angle and All-Cause Mortality

In 124 (30%) patients, a planar QRS-T angle smaller or equal to 90° was measured on the baseline ECG. As summarized in Table 1, patients with a narrow planar QRS-T angle were more likely to be younger (61±11 year versus 64±10 years, P<0.05), to have a better LVEF (28±7% versus 25±7%, P<0.001), and shorter QRS duration (120±29 ms versus
The HR of a planar QRS-T angle >90° for mortality was 3.1 (95% CI, 1.3 to 7.3) as compared with patients with a narrow planar QRS-T angle. The cumulative event-free follow-up for all-cause mortality in patients with a wide spatial QRS-T angle was 99% (95% CI, 98 to 100) at 4 years of follow-up (Figure 1).

Fifty-six (14%) patients had a baseline spatial QRS-T angle smaller than or equal to 100°. These patients were younger, had a more preserved LVEF (30 ± 6% versus 26 ± 7%, P < 0.01) and a shorter QRS duration (115 ± 28 ms versus 132 ± 33 ms, P < 0.01), used statins more often (95% versus 83%, P < 0.05), and were using amiodarone less frequently (2% versus 16%, P < 0.01) (Table 1). As shown in Table 2, patients with a wide spatial QRS-T angle exhibited an HR for all-cause mortality of 1.7 (95% CI, 0.6 to 4.9).

QRS-T Angle and Ventricular Arrhythmia
The HR of a planar QRS-T angle wider than 90° for the occurrence of ventricular arrhythmia triggering appropriate device therapy was 2.9 (95% CI, 1.4 to 6.1). When adjusted for age, sex, LVEF, and QRS duration, the HR was 2.4 (95% CI, 1.1 to 5.2). Furthermore, this group demonstrated an almost 3-fold risk increase (HR, 2.9; 95% CI, 1.6 to 5.0) for the composite end point of appropriate therapy and mortality (Table 2). The cumulative event-free follow-up for appropriate therapy in patients with a narrow planar QRS-T angle was 95% (95% CI, 90 to 100) at 1 year, 93% (95% CI, 87 to 98) at 2 years, and 89% (95% CI, 81 to 98) at 4 years of follow-up (Figure 2).

As is shown in Table 2, patients with a wide spatial QRS-T angle exhibited a nearly 10-fold risk for the occurrence of ATP or shocks (HR, 9.9; 95% CI, 1.4 to 71.7) during follow-up. When adjusted for age, sex, LVEF, and QRS duration, the HR was 7.3 (95% CI, 1.0 to 53.8). Strikingly, the cumulative event-free follow-up for ventricular arrhythmia that triggered device therapy was 100% at 2 years and 96% (95% CI, 87 to 100) at 4 years of follow-up, as seen in Figure 2.
Identification of Patients Free of Life-Threatening Arrhythmias

Evaluation of the usefulness of a planar QRS-T angle $\leq 90^\circ$ at baseline in the prediction of an appropriate therapy-free follow-up revealed a positive predictive value of 94% (95% CI, 89 to 98) and a negative predictive value of 17% (95% CI, 12 to 21).

The spatial QRS-T angle had a positive predictive value of 98% (95% CI, 95 to 100) and a negative predictive value of 15% (95% CI, 12 to 19) for the prediction of an appropriate therapy-free follow-up. Most importantly, only 2% of the patients with a spatial QRS-T angle $\leq 100^\circ$ had appropriate device discharges during follow-up, the only event occurring after 745 days (Figure 2).

Discussion

In the current study, on the clinical application of the planar and spatial QRS-T angle in the prediction of ventricular arrhythmias in ischemic primary prevention ICD patients, the main findings can be summarized as follows: after adjustment for age, sex, LVEF, and QRS duration, (1) patients with a wide planar QRS-T angle exhibited a nearly 2.5-fold risk for mortality, as well as for appropriate device therapy; (2) patients with a wide spatial QRS-T angle had a 7-fold risk for ventricular arrhythmias triggering appropriate device therapy; and (3) patients with a spatial QRS-T $\leq 100^\circ$ before implantation, exhibited an absolute risk of 2% for appropriate therapy during follow-up.

With primary prevention ICD therapy as a class I indication in international guidelines in patients with a low LVEF, the indicated population, and therefore the worldwide defibrillator implantation rates, has increased significantly. This expansion is of such magnitude that health care systems might lack the logistic capacity and financial means to meet the demand of ICD implantations. Furthermore, MADIT II demonstrated a cumulative incidence of the need for

<table>
<thead>
<tr>
<th>Planar QRS-T Angle $\leq 90^\circ$, n/N (%)</th>
<th>Adjusted HR (95% CI)*</th>
<th>Spatial QRS-T Angle $\leq 100^\circ$, n/N (%)</th>
<th>Adjusted HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>8/124 (6.5)</td>
<td>48/288 (16.7)</td>
<td>2.9 (1.4–6.1)</td>
<td>1/56 (1.8)</td>
</tr>
<tr>
<td>6/124 (4.8)</td>
<td>40/288 (13.9)</td>
<td>3.1 (1.3–7.3)</td>
<td>4/56 (7.1)</td>
</tr>
<tr>
<td>14/124 (11.3)</td>
<td>82/288 (28.5)</td>
<td>2.9 (1.6–5.0)</td>
<td>5/56 (8.9)</td>
</tr>
</tbody>
</table>

*Hazard ratio was adjusted for age, sex, LVEF, and QRS duration.
Moreover, 6% of ICD-treated patients have severe device-related adverse events. These issues underscore the need for better risk stratification within the indicated population.

Ideally, a parameter for the identification of a population at high or at low risk for the need for defibrillator backup should be noninvasive and easily acquired. An ECG-derived parameter such as the QRS-T angle, validated in the current analysis, would fit these demands.

Risk Stratification With the QRS-T Angle

The QRS-T angle is the angle between the electric axes of depolarization and repolarization. In the present study, clinical application of both the planar as well as the spatial QRS-T angle has been investigated in primary prevention ICD recipients with ischemic heart disease. The planar QRS-T angle is the projection of the spatial QRS-T angle in the frontal plane. As with any projection, it is sensitive to variations of the anatomic position of the heart in thorax. Therefore, the spatial QRS-T angle, which is calculated in the plane that the QRS- and T-axes form, is a more robust clinical tool. This is an important issue because the results from this study demonstrate that a narrow spatial angle is associated with a lower risk of ventricular arrhythmias. Although the spatial QRS-T angle cannot be derived directly from the surface ECG, recent studies have provided easy methods to acquire the spatial QRS-T angle from the standard 12-lead ECG.

In our population of ischemic primary prevention ICD recipients, patients with a wide planar QRS-T angle demonstrated a HR of 2.5 for the need for defibrillator backup and 3.1 for all-cause mortality. In the recently published post hoc analysis of the DEFINITE trial by Pavri et al., the planar QRS-T angle was analyzed as a predictor of the composite end point of appropriate device therapy, mortality, and resuscitated cardiac arrest in a population with nonischemic cardiomyopathy. In this study, the HR of a planar QRS-T angle wider than 90° for the occurrence of appropriate device therapy was 1.95 (95% CI, 1.24 to 3.08). The HR for all-cause mortality was 1.81 (95% CI, 1.04 to 3.13).

After adjustment for other commonly used risk factors, the presence of a spatial QRS-T angle wider than 100° was associated with an HR of 7.3 for the occurrence of device therapy for ventricular arrhythmias as compared with patients with a spatial QRS-T angle ≤100°, in our population. More importantly, all patients with a spatial QRS-T angle ≤100° were free of device-generated therapy during 2 years after implantation. This indicates that the spatial QRS-T angle may have an important potential for risk stratification in patients with ischemic heart disease.

Previous studies on the spatial QRS-T angle have already indicated its high value in the risk stratification for cardiac death in a population without ICDs. In a large cohort of patients, Yamazaki et al. observed an HR of 1.9 (95% CI, 1.7 to 2.1) on cardiovascular death for a spatial QRS-T angle >100° after correction for other ECG parameters.
As a consequence of the balanced regulation of electric activation and recovery of the ventricles, a narrow QRS-T angle is generally observed in healthy individuals. Ventricular scar or residual ischemia, which is the arrhythmic substrate in ischemic cardiomyopathy, causes an imbalance of this process, sometimes referred to as electric heterogeneity or discordance of depolarization and repolarization. Vectorcardiographically, these alterations in cardiac electrophysiology become, among others, apparent through directional changes of the QRS and T vectors and consequent widening of the QRS-T angle. When patients with ischemic cardiomyopathy have a narrow QRS-T angle, which is then associated with electric homogeneity, it could be postulated that the amount of arrhythmic substrate is limited and may even be absent. The high incidence of ventricular arrhythmias in patients with a wide QRS-T angle and the low incidence in patients with a narrow QRS-T angle, as observed in the current study, underscores this principle.

Clinical Implications
Several noninvasive parameters that could improve patient selection for ICD therapy have been proposed. These include LVEF, QRS duration, QT interval, heart rate variability, ventricular ectopy on ambulatory monitoring, exercise capacity, and T-wave alternans. In addition, total cosine R to T, which is also a measure of QRS-T concordance like the QRS-T angle, has been proven a promising parameter in the mortality risk stratification in patients after myocardial infarction. However, this variable has not been assessed in an ICD-treated population, to our knowledge. Although the majority of these parameters appear promising, only LVEF has proven its usefulness in patient selection for ICD implantation and is currently the most important factor in the clinician’s choice whether or not an ICD is indicated. Still, in the implanted ischemic population, identified as being at high risk for ventricular arrhythmia based on depressed LVEF, 35% of patients actually have appropriate device therapy during follow-up, prompting the identification of a subpopulation at low risk. In our population of ischemic primary prevention ICD recipients, patients with a spatial QRS-T angle ≤100° demonstrated no ventricular arrhythmias during the first 2 years after implantation and only 2% during further follow-up. These results imply that this parameter could be used in the discrimination of patients in whom the beneficial effects of an ICD might not exceed the costs and potential morbidity accompanying ICD therapy.

Limitations
This was a nonrandomized, prospective, observational study, performed to assess the long-term follow-up in ischemic primary prevention ICD recipients and to assess the value of the planar and spatial QRS-T angle in baseline risk stratification. Adjustment for additional variables in the multivariable Cox model was limited by the number of end points reached. Furthermore, some patients without therapy during study follow-up might have reached an end point, had follow-up been longer. Additionally, because not all patients had postmortem ICD interrogation, some cases of death might have been arrhythmic. Finally, because patients were included over a period of 11 years, expanding guidelines for the implantation of defibrillators, treatment of acute myocardial infarction, and pharmacological antiarrhythmic therapy could have created an inhomogeneous population.

Conclusion
In patients with ischemic heart disease who are currently indicated for primary prevention ICD therapy, a baseline spatial QRS-T angle >100° is associated with a 7-fold risk for the occurrence of appropriate device therapy, even after adjustment for commonly used risk factors. More importantly, a spatial QRS-T angle ≤100° on the ECG before implantation can identify patients with very low risk of life-threatening ventricular arrhythmias in whom the beneficial effect of ICD treatment might not exceed the costs and potential complications.

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References


**CLINICAL PERSPECTIVE**

A depressed left ventricular ejection fraction identifies a large number of high-risk patients who receive implantable cardioverter-defibrillators for primary sudden death prevention. The minority, however, will have an appropriate therapy for ventricular tachycardia/fibrillation, and a similar number may have complications or unnecessary therapy (often shocks). Thus, there remains a need for better risk stratification to identify patients likely to benefit. This investigation evaluated the ECG-derived QRS-T angle for predicting spontaneous arrhythmias and mortality in an observational study of 412 primary prevention defibrillator recipients with ischemic heart disease and a left ventricular ejection fraction ≤40%. A widened spatial QRS-T angle predicted spontaneous ventricular tachycardia/fibrillation, with an adjusted hazard ratio of 7.3. Interestingly, in patients with a spatial QRS-T angle ≥100°, the incidence of life-threatening arrhythmias was as low as 2% during study follow-up. Similar characteristics were observed for the planar QRS-T angle, which is the frontal projection of the QRS-T angle but with lower discriminative power (adjusted hazard ratio, 2.9). Further study of the spatial QRS-T angle for risk stratification is warranted.
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