

Spatial QRS-T angle predicts cardiac death in a clinical population

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OBJECTIVES/BACKGROUND The purpose of this study was to validate the prognostic value of computer-derived measurements of the spatial alignment of ventricular depolarization and repolarization from the standard 12-lead ECG in a general medical population.

METHODS Analyses were performed on the first ECG digitally recorded from 46,573 consecutive patients since 1987. QRS and T vector were synthesized by deriving XYZ leads from the 12 leads using the inverse Dower weighting matrix. Subset analyses were considered in patients with and those without standard ECG diagnoses (i.e., atrial fibrillation, Q waves, left ventricular hypertrophy, prolonged QRS duration). The main outcome measure was cardiovascular mortality.

RESULTS During a mean follow-up of 6 years, 4,127 cardiovascular deaths occurred. After adjusting for age, heart rate, and gender in a Cox regression analysis, spatial QRS-T angle was the most significant predictor of cardiovascular mortality, outperforming all other ECG measurements and diagnostic statements. In the subset with ECGs free of any standard diagnoses, annual cardiovascular mortality was 0.8% for normal (0–50°), 2.3% for borderline (50–100°), and 5.1% for abnormal (100–180°) QRS-T angle groups. The borderline and abnormal angle groups had 1.5- and 1.9-fold higher risk, respectively, relative to the normal QRS-T angle group after adjustment for age, gender, and heart rate. Similar results were found when patients with standard ECG diagnosis were included or compared.

CONCLUSIONS Spatial QRS-T angle is a significant and independent predictor of cardiovascular mortality that provides greater prognostic discrimination than any of the commonly utilized ECG diagnostic classifications.

KEYWORDS Electrocardiography; Epidemiology; Mortality; Prognosis, QRS-T angle
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Introduction

Abnormalities of either ventricular depolarization or repolarization on standard 12-ECG can predict cardiovascular mortality. QRS duration is a measure of ventricular depolarization, whereas the ST segment and T wave of the QT interval represent the repolarization phase. Depolarization abnormalities reflect ventricular structural abnormalities (i.e., damage and hypertrophy), whereas repolarization abnormalities represent heterogeneities associated with electrical instability and sudden death. Combining both phenomena should optimize prognostication. The spatial QRS-T angle, defined as the angle between the directions of ventricular depolarization and repolarization, was recommended years ago by vector cardiographers

as such a combined measurement.^{1,2} More recently, the global angle between QRS wave and T wave was demonstrated to risk stratify postmyocardial infarction patients.³ In a population screening study, a divergent spatial angle was a stronger predictor than any of the classic cardiovascular risk factors or ECG risk indicators for predicting cardiovascular and sudden death.⁴ However, its optimal threshold for clinical utility for risk stratification is uncertain. This study was performed to examine the long-term prognostic impact of the spatial QRS-T angle relative to other ECG findings in a large general medical population and to develop practical thresholds for clinical application.

Methods

All ECGs obtained at the Palo Alto VA Medical Center between March 1987 and December 2000 were digitally recorded and stored in the General Electric MUSE ECG

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(Received August 15, 2004; accepted October 22, 2004.)

management system (www.gemedicalsystems.com). Each ECG was labeled with the patient's social security number. When a patient had more than one ECG in the database, only the earliest ECG was considered. Computerized features from the ECG and several computerized ECG interpretations were extracted. ECGs obtained in an inpatient or outpatient setting, or in the emergency room, were coded separately because they could be influenced by acute clinical events. ECGs exhibiting electronic pacing ($n = 309$) or Wolff-Parkinson-White syndrome ($n = 44$) were excluded from the analyses. Standardized computerized ECG criteria as described by the General Electric 12-lead ECG analysis program were utilized for diagnostic Q waves and bundle branch blocks (see MUSE/12 lead ECG physician program manual at www.gemedicalsystems.com). Although these interpretations usually are overread by a cardiologist before they are released as "confirmed," we used only the computer interpretation. ST-segment and T-wave patterns were categorized based on the Minnesota code [4-1 and 4-2 as major ST depression; 4-3 as minor ST depression; 5-1, 5-2 as major T abnormality; 5-3 and 5-4 as minor T abnormality].⁵ Left ventricular hypertrophy was defined as >3 using the Romhilt-Estes point score.⁶ T-axis abnormality in the frontal plane was defined based on a previous study.⁷ Pathologic Q waves were considered present if ≥ 40 ms and $\geq 25\%$ of the amplitude in the following R wave in adjacent leads in each area (inferior, anterior, lateral). The Cardiac Infarction Injury Score^{8,9} also was calculated. QT dispersion was not considered because it is a poor independent predictor of cardiovascular mortality.¹⁰ The spatial axes where the maximal amplitudes of the QRS and T vectors were synthesized by deriving orthogonal XYZ leads from the 12 leads using the inverse Dower weighting matrix.^{11,12} Spatial QRS-T angle, the angle between the ventricular depolarization (QRS) and repolarization (T wave), was computed.

A subset was created by excluding ECGs exhibiting atrial fibrillation, diagnostic Q waves, left ventricular hypertrophy, QRS duration >120 ms, left bundle branch block, and right bundle branch block, and intraventricular conduction delay. This subgroup without standard ECG diagnosis consisted of 35,008 patients; the remaining patients ($n = 11,565$) with abnormal ECGs were considered separately.

Both the Social Security death index and the California Health Department Service were used to ascertain vital status as of December 30, 2000. The main outcome measure was cardiovascular mortality obtained from death certificates.

Statistical analysis

The database was imported into NCSS (Number Cruncher Statistical System, Kaysville, UT, USA) for analysis. Descriptive statistics were used to determine mean values for continuous variables and to test for normality. Differences in characteristics among the groups were compared using Chi-square tests, nonpaired t-tests, and analysis of variance, as appropriate.

Post hoc procedures were performed with the Bonferroni test. $P < .05$ was considered significant.

Cox proportional hazard testing was performed to assess the significance and independence of predictors of cardiovascular mortality, adjusted for age, gender, and heart rate. QRS-T angle in the group with no standard ECG diagnosis and other established ECG indicators were considered in the analysis. Multivariate analyses included QRS duration, frontal T axis, major T-wave change (MC 5-1, 5-2), minor T-wave change (MC 5-3, 5-4), major ST depression (MC 4-1, 4-2), and minor ST depression (MC 4-3). The entire analysis was repeated in the abnormal ECG group with the common ECG abnormalities and indicators, and in women only. The subset analysis was repeated only in outpatients in order to exclude ECGs even possibly associated with acute clinical events.

Relative risks were calculated for various degrees of QRS-T angles to determine criteria for practical clinical utility. Relative risk of each angle was calculated to demonstrate incremental risk per each incremental step, then spatial QRS-T angle was categorized into three groups: normal ($0-50^\circ$), borderline ($50-100^\circ$), and abnormal ($100-180^\circ$). Kaplan Meier survival curves were plotted accordingly and compared using the log rank test.

Results

Baseline demographics based on QRS-T angle classification

During a mean follow-up of 6 years, a total of 4,127 cardiovascular deaths occurred. Table 1 presents baseline characteristics of the total study population comparing those with normal ($0-50^\circ$), borderline ($50-100^\circ$) and abnormal ($100-180^\circ$) spatial QRS-T angles as determined using the derived XYZ leads. Mean QRS-T angle was greater in men than women (men 44.8 ± 29.2 vs women 33.2 ± 27.0 , $P < .001$). The spatial QRS-T angle was strongly associated with age, heart rate, and QRS duration. Minor ST and/or T changes were more prevalent among those with a borderline QRS-T angle, whereas major ST and/or T change were predominant among patients with abnormal angles. Similar findings were observed among patients in the abnormal ECG group. A large QRS-T angle was associated with other ECG indicators and criteria, such as atrial fibrillation, left ventricular hypertrophy, and left and right bundle branch block. These ECG abnormalities were more prevalent among patients with greater QRS-T angles. Similar findings were observed when patients with and without any standard ECG diagnosis were considered.

Cox analysis

Adjusting for age, gender, and heart rate in the Cox analysis, the spatial QRS-T angles and other ECG indicators

Table 1 Demographic and clinical characteristics of the total population

	Total	Spatial QRS-T angle			Over all <i>P</i>
		Normal (0–50°)	Borderline (50–100°)	Abnormal (100–180°)	
Number	46,573	32,380 (69.5)	11,257 (24.2)	2,936 (6.3)	
Cardiovascular death	4,127	1,734 (5.4)	1,592 (14.1)	801 (27.3)	
Female	4,600 (9.9)	3,806 (11.7)	614 (5.5)	180 (6.1)	<.001
Age	56.8 ± 14.7	55.6 ± 14.7	59.8 ± 14.1*	65.6 ± 11.5*†	<.001
Body mass index	27.2 ± 5.5	27.1 ± 5.5	27.5 ± 5.5*	27.2 ± 5.4	<.001
Inpatient	12,824 (27.5)	8,343 (25.8)	3,329 (29.6)	1,152 (39.2)	.001
Heart rate (bpm)	74.1 ± 16.5	72.8 ± 15.6	76.8 ± 17.4*	78.8 ± 19.8*†	<.001
QRS duration (ms)	95.2 ± 16.6	92.9 ± 13.6	98.2 ± 18.9*	109.4 ± 25.5*†	<.001
Minor T-wave change (MC5–3,5–4)	6,255 (13.4)	2,298 (7.1)	3,658 (32.5)	299 (10.2)	<.001
Major T-wave change (MC5–1,5–2)	3,663 (7.9)	351 (1.1)	1,492 (13.3)	1,820 (62.0)	<.001
Minor ST change (MC4–3)	22,939 (49.3)	16,717 (51.4)	5,436 (48.3)	786 (26.8)	<.001
Major ST change (MC4–1,4–2)	6383 (13.7)	3,082 (9.5)	2,040 (18.1)	1,261 (42.9)	<.001
Atrial fibrillation	1,332 (2.9)	497 (1.5)	536 (4.8)	299 (10.2)	<.001
Left ventricular hypertrophy	2,098 (4.5)	649 (2.0)	867 (7.7)	582 (19.8)	<.001
Pathologic Q wave	5,787 (12.4)	2,677 (8.3)	2,228 (19.8)	882 (30.0)	<.001
QRS duration >120 ms					
Left bundle branch block	625 (1.3)	34 (0.1)	280 (2.5)	311 (10.6)	<.001
Right bundle branch block	1,675 (3.6)	894 (2.8)	525 (4.7)	256 (8.7)	<.001
Intraventricular conduction delay	1,476 (3.2)	827 (2.6)	477 (4.2)	172 (5.9)	<.001
T-wave amplitude in limb lead I	1.6 ± 1.3	2.0 ± 1.0	0.90 ± 1.1*	−0.68 ± 1.3*†	<.001
Cardiac Infarction Injury Score	13.7 ± 10.5	11.3 ± 9.3	18.2 ± 10.6*	23.5 ± 10.8*†	<.001

MC = Minnesota code.

**P* < .05 vs normal group; †*P* < .05 vs borderline group.

and measurements were considered univariately. Spatial QRS-T angle was significantly and strongly associated with cardiovascular death. In the subgroup without any standard ECG diagnosis, borderline and abnormal QRS-T angle had hazard ratios of 1.9 (CI 1.7–2.1) and 3.6 (CI 3.0–4.2) respectively, whereas the hazard ratios were 1.7 (CI 1.6–1.9) and 2.4 (CI 2.2–2.7) for the borderline and abnormal QRS-T angles, respectively, for the abnormal ECG group (*P* < .0001 for all). When the genders were considered separately, similar results were obtained: borderline and abnormal QRS-T angle, hazard ratios of 2.1 (1.9–2.2) and 3.4 (3.1–3.8), respectively, for men; hazard ratios of 2.6 (1.9–3.6) and 4.7 (3.2–6.7) for women. Major ST or major T abnormalities and QRS duration were associated with mortality in both the subgroup without any standard ECG diagnosis and those with abnormal ECGs. Pathologic Q waves, left ventricular hypertrophy, and prolonged QRS duration (>120 ms) also were significant predictors of cardiovascular death in the abnormal ECG group.

Relative risk of various QRS-T angles and optimal cutpoint for clinical utilization

Cutpoints were determined after reviewing a plot of the hazard for each 10° and 10 percentile increase in angle divergence. Figure 1 illustrates the relative risks of each 10 percentile for the spatial QRS-T angle thresholds plotted using the first decile of angle of 0 to 14° as the reference group, with age, gender, and heart rate adjust-

ment. Risk increased progressively as the angle diverged, with the greatest relative risks occurring when the spatial angle was the most divergent (5 percentile) at greater than 107° [3.9 (CI 3.5–4.4, *P* < .0001)]. Hazard plots of each 10 degree also were considered in similar fashion, and such angle division demonstrates the most critical threshold was 100° and the most practical threshold for clinical utility.

When all available T wave components were considered, including Minnesota code, T wave amplitude in 11 leads (excluding aVR), frontal T axis, and spatial T-wave angle, T-wave amplitude in limb lead I was chosen as the most significant predictor. However, its significance was interchanged when spatial QRS-T angle was included. The spatial QRS-T angle was entered into multiple analyses to

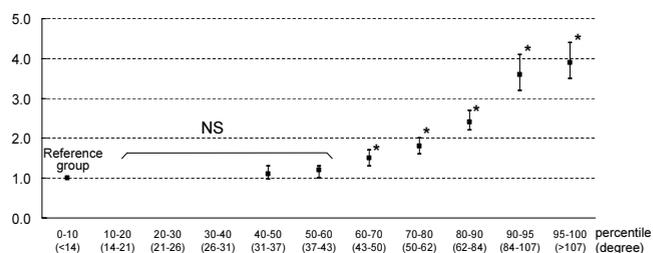


Figure 1 Relative risk with 95% confidence intervals of 10 percentile increase in angle divergence of spatial QRS-T angle with age, gender, and heart rate adjustment. The first decile of QRS-T angle (<14°) was considered the reference group. **P* < .001 vs reference group.

Table 2 Hazard ratios of spatial QRS-T angle for cardiovascular death after adjustment for standard ECG measurements and indicators in the total study population

Variable	Hazard ratio (95% CI)	P value
Spatial QRS-T angle		
Abnormal group (100–180°)	1.9 (1.7–2.1)	<.0001
Borderline group (50–100°)	1.5 (1.4–1.6)	<.0001
Pathological Q wave	1.4 (1.3–1.5)	<.0001
QRS duration >120 ms	1.9 (1.7–2.1)	<.0001
Cardiac Infarction Injury Score (>30)	2.2 (1.8–2.7)	<.0001
Left ventricular hypertrophy	1.4 (1.3–1.6)	<.0001
Major ST change (MC4–1, 4–2)	1.1 (1.1–1.2)	<.0001
Atrial fibrillation	1.2 (1.1–1.4)	<.0001
Major T-wave change (MC5–1, 5–2)	1.5 (1.3–1.7)	<.0001
Minor T-wave change (MC5–3, 5–4)	1.3 (1.2–1.4)	<.0005
Minor ST change (MC4–3)	—	NS

Data are from Cox proportional hazards analysis with age, gender, and heart rate adjustment. Variables are listed in the order of the model selection.

MC = Minnesota Code.

determine its interaction with other standard ECG features. Table 2 presents the results in the total population with the variables listed in order of selection. Spatial QRS-T angle was a significant and independent predictor of cardiovascular death, outperforming other ECG measurements. Similar results were obtained in the subgroup without any standard ECG diagnosis and the abnormal subgroup, as well as among outpatients and women.

Multivariate comparisons with other ECG measurements

Kaplan-Meier survival curves

Figure 2 illustrates the survival plots for the cutpoints of the spatial QRS-T angle. A significant separation was demonstrated among the different QRS-T angle categories in both ECG subgroups ($P < .0001$). The annual cardiovascular mortality among subjects with an abnormal QRS-T angle was 4.0% in the subgroup without any standard ECG diagnosis and 5.6% in the abnormal ECG group, whereas the annual cardiovascular mortalities associated with a QRS-T angle $<50^\circ$ were 0.6% and 1.6% for the subgroup without any standard ECG diagnosis and the abnormal ECG group, respectively.

A similar association between QRS-T angle and cardiovascular mortality was seen when considering subjects with specific ECG abnormalities, including pathologic Q waves, left ventricular hypertrophy, atrial fibrillation, and prolonged QTc ($P < .0001$ for all; Figure 3). Figure 4 illustrates ECGs with prolonged QRS duration. Among the three categories of wide QRS duration, intraventricular conduction delay had the most remarkable differences in mortality (1.1% annual mortality for normal QRS-T angle vs 7.9 for an abnormal angle). The spatial QRS-T angle provided additional risk information in each individual subgroup of

ECG categories except for left bundle branch block, in which a wide spatial angle reflected opposing directions of the QRS complex and T wave.

Discussion

The current study validates the utility of QRS-T spatial angle in predicting cardiovascular mortality in a large, general hospital-based population. Our findings support the value of repolarization measures^{13–15} as determined by the spatial QRS-T angle as a tool for risk stratification. Although considered a marker of pathology from the early days of ECG, to the best of our knowledge, this study is the first to report the optimal cutpoint for utilizing the spatial QRS-T angle clinically.

Previous studies demonstrated other angular repolarization abnormalities to be significant and independent predictors for cardiovascular disease. Kors et al⁷ investigated the prognostic importance of the frontal T axis, using ECGs from 5,781 men and women aged 55 years and older from a prospective population-based study. Participants with an abnormal frontal plane T axis, defined as the range from 105 to 180° and –180 to –15° (11%), had an increased risk for cardiac events and death. Zabel et al¹⁶ studied the prognostic value of T-wave morphology descriptors derived from the resting standard 12-lead ECG in male veterans with cardiovascular disease. The total cosine R-to-T angle (global angle between repolarization and depolarization) and T-wave loop dispersion were considered in the Cox regression analysis, and both were independently associated with clinical events. Rautaharju et al¹⁷ focused on the spatial T-axis deviation in 4,173 subjects considered free of cardiovascular disease. The prevalence of marked T-axis deviation ($>45^\circ$ from the reference vector) was 12%. Adjusting for clinical risk factors and other ECG abnormalities, there was a nearly twofold excess risk of cardiovascular death and an approximate 50% excess risk of cardiovascular and all-cause mortality for those with marked T-axis deviation.

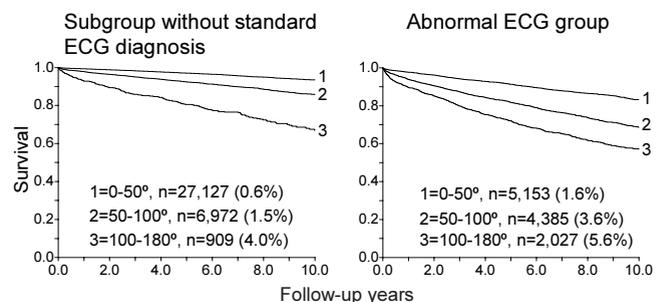


Figure 2 Kaplan-Meier survival curves for cutpoint of spatial QRS-T angle in the subgroup without any abnormal standard ECG diagnosis and the abnormal ECG group. Numbers in parentheses are annual mortalities. Abnormal ECG was defined as atrial fibrillation, left ventricular hypertrophy, pathologic Q wave, and/or QRS duration >120 ms.

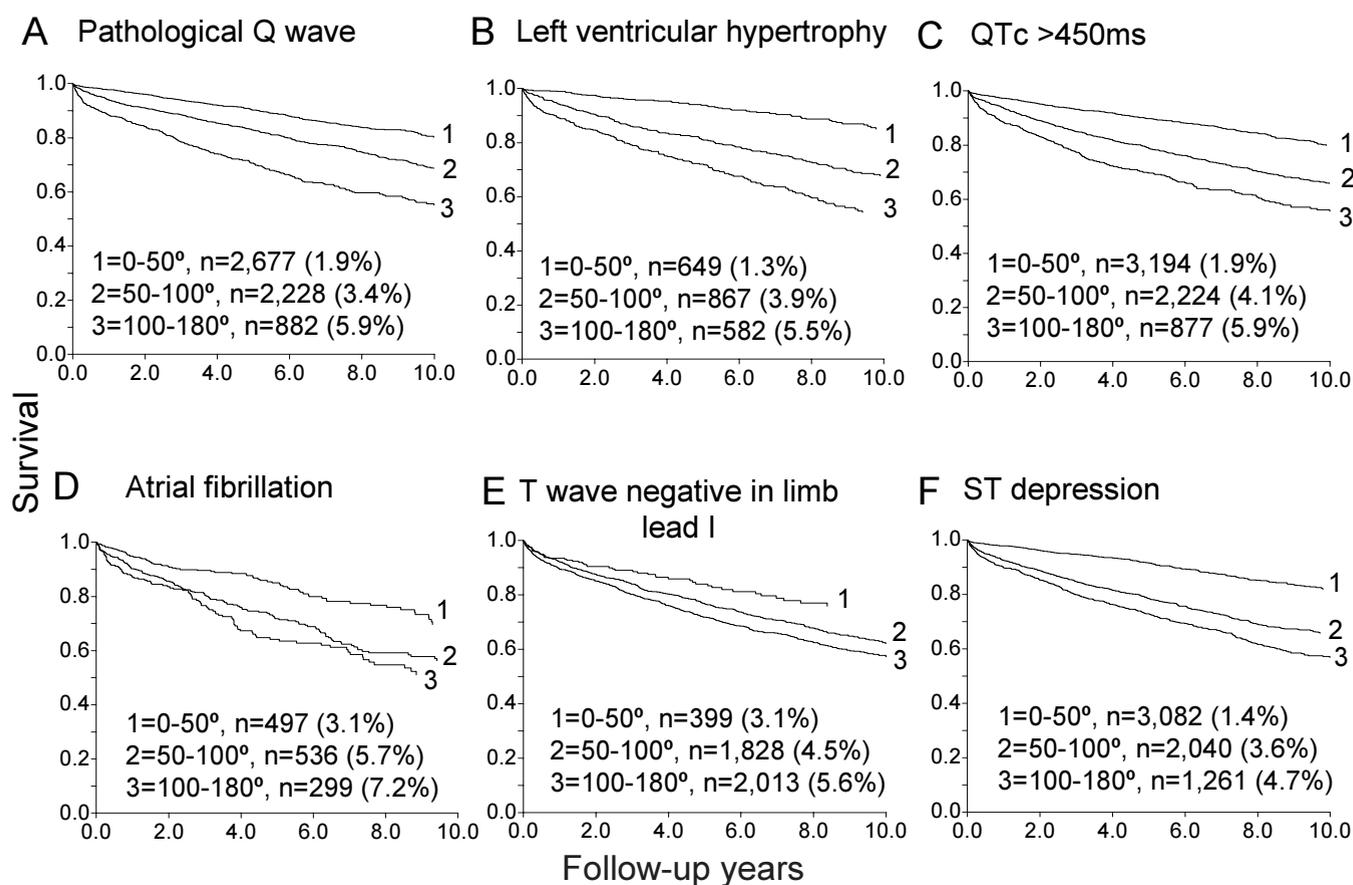


Figure 3 Kaplan-Meier survival curves for cutpoint of spatial QRS-T angle in individual ECG abnormalities. Subject with pathologic Q wave (A), left ventricular hypertrophy (B), QTc >450 ms (C), atrial fibrillation (D), T wave negative in limb lead I (E), and ST depression (F). Numbers in parentheses are annual mortalities.

The spatial QRS-T angle has been considered in cross-sectional studies in relation to cigarette smoking, recent and old myocardial infarction, and blood pressure control among hypertensives.¹⁸⁻²⁰ The studies demonstrate that abnormal spatial angles are associated with these risk factors. Most recently, investigators from The Netherlands demonstrated the spatial QRS-T angle was a strong and independent predictor of cardiac death.⁴ In the prospective Rotterdam Study, 6,134 men and women aged 55 years or older were categorized as having normal (0-105°), borderline (105-135°), or abnormal (135-180°) spatial QRS-T angles.⁴ Abnormal angles independently predicted multiple cardiac endpoints including sudden death (hazard ratio 5.2).

Study limitations

Our study considered men and women, and our ECGs represent a broad sample from inpatients and outpatients with ECGs obtained according to clinical practice. Results of diagnostic tests, such as echocardiograms or cardiac catheterization, are not available; therefore, events such as myocardial infarction, heart failure, and coronary heart disease cannot be considered. Incorporating other tests or using test results as surrogate endpoints would bias our results

because these tests are performed for specific clinical indications. Data on the classic risk factors are not available but have adjusted for age, gender, and heart rate. The cutpoints chosen may differ in other populations with varying pretest probabilities of death. Cardiovascular mortality was determined by death certificates. Death certificates have their limitations, but in general they classify deaths as accidental, gastrointestinal, pulmonary, cancer, renal failure, diabetes complications, infectious diseases, sepsis, and multiorgan failure, so the remaining deaths most likely result from cardiovascular causes. This endpoint is more appropriate as a test for cardiovascular disease. Although all-cause mortality is a more important endpoint for intervention studies, cardiovascular mortality is more appropriate for evaluating a cardiovascular test (i.e., the ECG).

Extended retrospective studies may be less relevant as illustrated by the finding that the incidence of out-of-hospital cardiac arrest (about half of cardiac deaths in most studies) decreased from 26.3 per 100,000 from 1985 to 1989 to 7.7 per 100,000 in 2000 to 2002.²¹ It also should be noted that (1) the spatial QRS-T vector can be easily calculated with modern computer-assisted ECG machines but usually is not available in routine reports, and (2) T-wave amplitude in the left precordial leads and

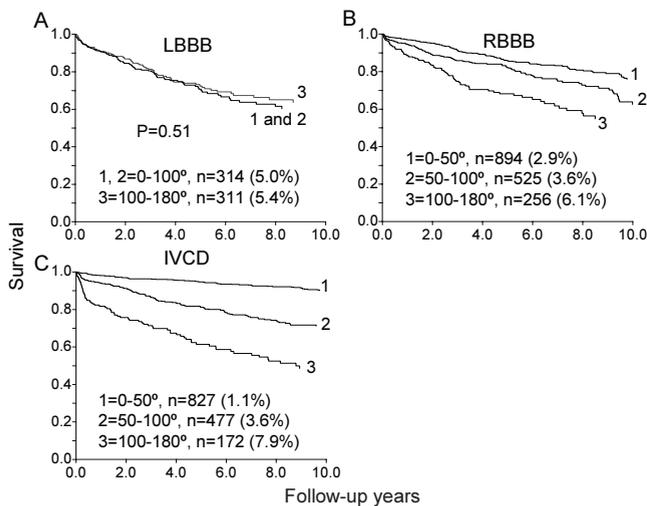


Figure 4 Kaplan-Meier survival curves for cutpoint of spatial QRS-T angle in ECGs with prolonged QRS duration. Subject with left bundle branch block (A), right bundle branch block (B), and intraventricular conduction delay (C).

the QRS-T angle in the horizontal plane are not included in the final Cox model.

Conclusion

The spatial QRS-T angle is a significant and independent predictor of cardiovascular death. It provides more information than any other established ECG characteristics and can easily be calculated as part of computerized ECG analysis. The standard ECG is widely available, playing a critical role in evaluation of possible and known cardiac disease. Spatial or vectorcardiographic assessment of the angle between the QRS and T-wave vectors offers unique information not obtained from conventional markers derived from standard ECG. We demonstrated that it can be used to further stratify patients with standard ECG abnormalities. Our findings confirm previous research regarding the prognostic value of spatial QRS-T angle and provide clinicians with cutpoints for its clinical application. The physician can apply these cutpoints to assist decision-making regarding further cardiac testing, the intensity of risk factor management, and/or referral to a cardiologist.

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