Principal Component Analysis of the T Wave and Prediction of Cardiovascular Mortality in American Indians

The Strong Heart Study

Peter M. Okin, MD; Richard B. Devereux, MD; Richard R. Fabsitz, MA; Elisa T. Lee, PhD; James M. Galloway, MD; Barbara V. Howard, PhD

Background—Increased QT interval dispersion (QTd) is a proposed ECG marker of vulnerability to ventricular arrhythmias and of cardiovascular (CV) mortality. However, principal component analysis (PCA) of the T-wave vector loop may more accurately represent repolarization abnormalities than QTd.

Methods and Results—Predictive values of QTd and PCA were assessed in 1839 American Indian participants in the first Strong Heart Study examination. T-wave loop morphology was quantified by the ratio of the second to first eigenvalues of the T-wave vector by PCA (PCA ratio); QTd was quantified as the difference between maximum and minimum QT intervals. After 3.7±0.9 years mean follow-up, there were 55 CV deaths. In univariate analyses, an increased PCA ratio predicted CV mortality in women (χ²=7.8, P=0.0053) and men (χ²=9.5, P=0.0021). In contrast, increased QTd was a significant predictor of CV mortality in women (χ²=30.6, P<0.0001) but not in men (χ²=2.0, P=NS). In multivariate Cox analyses controlling for risk factors and rate-corrected QT interval, the PCA ratio remained a significant predictor of CV mortality in women (χ²=4.0, P=0.043) and men (χ²=6.4, P=0.011); QTd was a significant predictor in women only (χ²=11.0, P=0.0009). PCA ratios >90th percentile (32% in women and 24.6% in men) identified women with a 3.68-fold increased risk of CV mortality (95% CI, 1.54 to 8.83) and men with a 2.77-fold increased risk (95% CI, 1.18 to 6.49).

Conclusions—Abnormalities of repolarization measured by PCA of the T-wave loop predict CV death in men and women, supporting use of PCA for quantifying repolarization abnormalities. (Circulation. 2002;105:714-719.)

Key Words: electrocardiography ● epidemiology ● mortality ● prognosis

Heterogeneity or dispersion of ventricular repolarization has been implicated in the genesis of ventricular arrhythmias1–4 and can be accurately determined with invasive monophasic action potential recordings.5–7 Complex body surface mapping techniques seem to provide accurate, non-invasive measures of dispersion of repolarization,8,9 providing an impetus for development of more widely applicable ECG measures of repolarization heterogeneity. Increased QT dispersion (QTd) on the 12-lead ECG has been linked to increased heterogeneity of ventricular repolarization, implicated in the genesis of ventricular arrhythmias, and associated with adverse prognosis in a variety of populations.10–12 However, the value of QTd remains clouded by uncertainties regarding the extent to which QT interval differences reflect true heterogeneity of repolarization as opposed to measurement variability that may in part be related to difficulties in accurate determination of T-wave offset.13–16

Theoretical and experimental studies suggest that ventricular repolarization occurs in a nonlinear and inhomogeneous fashion.1,3,6,8,16–18 As a consequence, spatial measures of repolarization that take into account T-wave complexity using principal component analysis (PCA) of the T-wave vector should be a more accurate and clinically useful surface ECG marker of heterogeneity of repolarization than simple scalar intervals from the ECG, such as QTd.7,14–16,19–22 Therefore, the present study examined the predictive value of PCA of the T-wave vector (PCA ratio) and simple QTd for cardiovascular mortality in both men and women in a prospective population-based study in which QTd has previously been demonstrated to be a significant predictor of cardiovascular mortality in the overall population.12

Methods

Study Population
The Strong Heart Study is a community-based study of cardiovascular disease and risk factors in American Indians from 13 communities in Arizona, Oklahoma, North Dakota, and South Dakota. Detailed information about the population and methods has previ...
T wave with a threshold defined by the T-P segment.20,21 Leads with offset from the intersection of the maximal slope of the terminal components.14,15,20

Principal Component Analysis

PCA is a method for characterizing or mathematically representing data that, when applied to T waves, derives features of repolarization in a manner that is less dependent on precise determination of T-wave offset. Previous studies of ventricular repolarization have reported that a T-wave offset.23 QTd interval measurements were performed using interactive software (QT-Guard, GE Medical Systems) that detects QRS

Electrocardiography

Standard 12-lead ECGs were performed with MAC-PC or MAC-12 digital ECG systems (GE Medical Systems), as previously described.12 QT interval measurements were performed using interactive software (QT-Guard, GE Medical Systems) that detects QRS onset and uses a least-squares fitting method to identify T-wave offset from the intersection of the maximal slope of the terminal T wave with a threshold defined by the T-P segment.20,22 Leads with high noise levels, flat T waves, and T waves with unidentifiable amplitudes were excluded from T-wave offset determinations.12 QT intervals were measured in all 12 leads and corrected for heart rate (QTC) with Bazett’s formula.24 QTd was calculated as the difference between the maximal and minimal QTC intervals.12

Principal Component Analysis

PCA is a method for characterizing or mathematically representing data that, when applied to T waves, derives features of repolarization in a manner that is less dependent on precise determination of T-wave offset. Previous studies of ventricular repolarization have demonstrated that the first component or eigenvector accounts for most of the energy in repolarization when applied to the normal T-wave vector, whereas inhomogeneous repolarization is indicated by a relevant contribution of the second and third components.14,15,20–22,25 Thus, the ratio of the second to first eigenvectors of the spatial T-wave vector generated from the 12-lead digital ECG (PCA ratio) was calculated as a measure of the complexity or heterogeneity of repolarization.14,15,20–22,25 The PCA ratio provides information that can be visualized by analogy as the long and short axes of the three-dimensional T-wave loop and provides an estimate of the relative fatness of the T-wave loop relative to its peak amplitude, in which a fatter loop with a higher PCA ratio reflects more complex T-wave morphology.15,23

Clinical Evaluation and Determination of End Points

All participants underwent a personal interview, Rose questionnaire,26 physical examination, and fasting blood and urine sampling and were categorized as having definite or possible coronary heart disease and as diabetic.23 Deaths were identified in an ongoing surveillance from sources in each community and through annual follow-up of each participant and were verified through death certificates and review of medical records. Deaths were classified as cardiovascular if caused by myocardial infarction, stroke, sudden death from coronary heart disease, or congestive heart failure by an independent review panel of physicians unaware of QTd and PCA findings.27

Data and Statistical Analyses

Data were analyzed with SPSS, release 9.0 (SPSS Inc). Mean values were compared between men and women using 2-way ANOVA to adjust for possible differences between centers. Proportions were compared by χ² tests. Mortality rates were calculated separately in men and women and were plotted according to the Kaplan-Meier product-limit method24; death rates were compared between groups with the log-rank test. Mortality analyses were performed by fitting Cox proportional hazards models to the data after stratification by center.29 The estimated relative risk of the incidence of cardiovascular death for positive compared with negative test outcomes was computed as the anti-log of the estimated coefficient for dichotomous variables.30 For continuous variables, the comparison in relative risk was computed for a one-SD-of-the-mean increase as the anti-log of the estimated coefficients multiplied by the SD. The 95% CI of each relative risk was calculated from the estimated coefficients and their SEs31 and Wald χ² statistics, and probability values were calculated. To test the independence of the PCA ratio and QTd as predictors of mortality, multivariate Cox models were used, including as covariates age, body mass index, diabetes, diastolic and systolic blood pressure, HDL and LDL cholesterol levels, triglyceride level, alcohol use, history of smoking or prevalent coronary heart disease, QTc interval, and study center. For all tests, a 2-tailed P value <0.05 was required.

Results

Patient Characteristics

After a mean follow-up of 3.7±0.9 years, there were 55 cardiovascular deaths. Clinical characteristics of the 1042 women and the 797 men included in the study are compared in Table 1. The women were slightly older, had higher body mass indexes, lower diastolic and systolic blood pressures, and IGT, impaired glucose tolerance.

Principal Component Analysis and Mortality

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Table 1. Clinical Characteristics, PCA Ratio, and QTd Measurements in Participants According to Sex

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men (n=797)</th>
<th>Women (n=1042)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55±8</td>
<td>56±8</td>
<td>0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.9±5.7</td>
<td>31.0±6.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>80±11</td>
<td>75±10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>129±19</td>
<td>126±21</td>
<td>0.009</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>42±12</td>
<td>47±13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>118±33</td>
<td>113±33</td>
<td>0.007</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>144±144</td>
<td>148±132</td>
<td>0.534</td>
</tr>
<tr>
<td>Albuminuria, log mg/g</td>
<td>2.59±2.11</td>
<td>2.96±2.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes or IGT, %</td>
<td>55.1</td>
<td>66.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prevalent CHD, %</td>
<td>10.7</td>
<td>13.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>17.6</td>
<td>17.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Never</td>
<td>39.8</td>
<td>41.8</td>
<td>28.5</td>
</tr>
<tr>
<td>Previous</td>
<td>40.6</td>
<td>21±14</td>
<td>22±19</td>
</tr>
<tr>
<td>PCA ratio, %</td>
<td>15.5±9.5</td>
<td>19.3±10.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV mortality, %</td>
<td>3.8</td>
<td>2.4</td>
<td>0.098</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; CHD, coronary heart disease; CV, cardiovascular; and IGT, impaired glucose tolerance.

Table 2. Univariate Cox Proportional Hazards Models for Prediction of Cardiovascular Disease Mortality in Men and Women, Examining QTd and PCA Ratio as Continuous Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Comparisons</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTd, ms</td>
<td>Women</td>
<td>19</td>
<td>1.59</td>
<td>1.35–1.86</td>
<td>30.6</td>
</tr>
<tr>
<td>Men</td>
<td>14</td>
<td>1.23</td>
<td>0.92–1.64</td>
<td>2.0</td>
<td>0.1555</td>
</tr>
<tr>
<td>PCA ratio, %</td>
<td>Women</td>
<td>10.7</td>
<td>1.49</td>
<td>1.13–1.97</td>
<td>7.8</td>
</tr>
<tr>
<td>Men</td>
<td>9.5</td>
<td>1.36</td>
<td>1.12–1.66</td>
<td>9.5</td>
<td>0.0021</td>
</tr>
</tbody>
</table>

*Adjusted for possible center effects.

†Relative risks calculated for a 1-SD increase in the mean.
higher HDL and lower LDL cholesterol levels, more albuminuria, and a greater prevalence of diabetes and possible coronary heart disease, and were more likely to have never smoked, but they did not differ with respect to serum triglyceride levels compared with men. Cardiovascular mortality was slightly but not significantly higher in men than in women. Mean QTd was nearly identical in men and women, but the PCA ratio was significantly greater in women than in men. The PCA ratio correlated only modestly with QTd in both women \((r=0.254, P<0.001)\) and men \((r=0.300, P<0.001)\).

**QTd and PCA Ratio and Prediction of Cardiovascular Mortality**

PCA ratio was a significant univariate predictor of cardiovascular mortality in both men and women, whereas QTd significantly predicted cardiovascular death in women only (Table 2). Assessment of the PCA ratio as a continuous variable revealed increases in cardiovascular mortality of 49\% in women and 36\% in men per 1-SD increase in PCA ratio across the entire range from low to normal to elevated PCA ratios. In contrast, although a 1-SD increase in QTd was associated with a nearly 60\% increased risk of cardiovascular mortality in women, increased QTd did not significantly stratify the risk of cardiovascular death in men. When participants were divided into groups on the basis of PCA ratios greater than the 90th percentile values in Strong Heart Study women (32.0\%) and men (24.6\%), values found to have >95\% specificity in a separate population of healthy subjects, both women and men with high PCA ratios had significantly greater cardiovascular mortality by Kaplan-Meier analyses (Figures 1 and 2). In women, a PCA ratio >32\% was associated with a 3.68-fold increased risk of cardiovascular death (95\% CI, 1.54 to 8.83) and an actuarial 5-year cardiovascular mortality of 11.4\% versus only 4.3\% in those with PCA ratios ≤32\%. In men, a PCA ratio >24.6\% was associated with a 2.77-fold increased risk of cardiovascular mortality (95\% CI, 1.18 to 6.49) and an actuarial 5-year cardiovascular mortality of 16.5\% compared with only 4.9\% in those with PCA ratios ≤24.6\%.

After adjustment for age, body mass index, diastolic and systolic blood pressures, HDL and LDL cholesterol, triglycer-
erides, albuminuria, alcohol use, prevalent diabetes or coronary heart disease, history of smoking, QTc interval, and study center. Priori et al\textsuperscript{15,32} found the PCA ratio to be significantly higher in long-QT syndrome patients than healthy subjects and to be more sensitive than scalar QTd measurements for the identification of repolarization abnormalities in these patients. DeAmbrogi et al\textsuperscript{9} demonstrated that PCA applied to body surface recording from 117 electrodes distinguished between normal and abnormal repolarization patterns with a sensitivity of 87% and a specificity of 96%. In a previous study of healthy subjects,\textsuperscript{25} we demonstrated a significant relationship between the PCA ratio and the sum of the T-wave area, a measure that significantly correlates with the dispersion of monophasic action potential duration at 90% recovery time and with dispersion of recovery time in isolated rabbit heart studies.\textsuperscript{7}

The present study additionally supports the application of the PCA ratio as a measure of repolarization heterogeneity for the prediction of cardiovascular mortality in both men and women. Even after controlling for multiple additional risk factors, the PCA ratio remained a significant predictor of cardiovascular death. In distinct contrast to the present findings, Zabel et al\textsuperscript{19} demonstrated lower PCA ratios in patients with arrhythmic events after myocardial infarction and that a lower PCA ratio achieved only borderline statistical significance for the prediction of arrhythmic events. However, these diametrically opposite results in the magnitude of the PCA ratio between patients with and without events and consequent differences in performance of the PCA ratio almost certainly reflect methodological differences in calculation of the PCA ratio. Zabel et al\textsuperscript{19} calculated the PCA ratio as the ratio of the second principal component to the square root of the sum of the squares of all 8 singular values, an approach that would decrease the magnitude of the PCA ratio in patients with greater complexity of repolarization in whom there are greater contributions of the second and higher components of repolarization. However, Zabel et al\textsuperscript{19} demonstrated that T-wave loop dispersion and other descriptors of T-wave morphology did independently predict arrhythmic risk.

The present study demonstrated significantly higher PCA ratios in women than men, reproducing similar findings in a separate population of healthy subjects.\textsuperscript{25} Gender differences in the PCA ratio can be attributed to the lower T-wave amplitudes and T-wave areas found in women despite similar or slightly longer durations of repolarization,\textsuperscript{1,33} which would on average result in higher ratios of the second to first eigenvalues in women than in men. Indeed, gender differences in the PCA ratio in healthy subjects disappeared after adjusting for differences in T-wave area and body mass index between men and women.\textsuperscript{25}

### Discussion

In a large, population-based prospective study, computerized ECG measurement of abnormalities of ventricular repolarization as quantified by principle component analysis of the T-wave vector loop predict cardiovascular death in both men and women. In contrast, simple QT dispersion is predictive of cardiovascular mortality in women only. These findings support the value of T-wave complexity as measured by the PCA ratio in noninvasive risk stratification.

### Principal Component Analysis and T-Wave Complexity

Ventricular repolarization is a complex series of events occurring nonuniformly in space and over time, with the ST segment and T wave on the surface ECG representing an integrated signal from multiple repolarization wave fronts.\textsuperscript{1,6} PCA quantifies the relative weight of various components of repolarization from the surface ECG.\textsuperscript{15,25,32} Applying PCA to the three-dimensional T-wave loop generated from the ECG, the first 2 components or eigenvectors of repolarization represent the principal plane of the T-wave loop. Thus, the greater the ratio of the second to first component, the wider the T-loop is relative to its maximal amplitude, with a wider loop relative to height thought to reflect a greater dispersion or heterogeneity of repolarization in space and time.\textsuperscript{15,32} Several findings support this concept.

Using a similar approach to analysis of orthogonal lead ECGs and taking the ratio of square root of the second to first eigenvalues as a measure of repolarization inhomogeneity, Badilini et al\textsuperscript{14} found a significantly higher ratio in a small group of patients after myocardial infarction than in healthy subjects. Priori et al\textsuperscript{15,32} found the PCA ratio to be significantly higher in long-QT syndrome patients than healthy subjects and to be more sensitive than scalar QTd measurements for the identification of repolarization abnormalities in these patients.\textsuperscript{15} DeAmbrogi et al\textsuperscript{9} demonstrated that PCA applied to body surface recording from 117 electrodes distinguished between normal and abnormal repolarization patterns with a sensitivity of 87% and a specificity of 96%. In a previous study of healthy subjects,\textsuperscript{25} we demonstrated a significant relationship between the PCA ratio and the sum of the T-wave area, a measure that significantly correlates with the dispersion of monophasic action potential duration at 90% recovery time and with dispersion of recovery time in isolated rabbit heart studies.\textsuperscript{7}

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### QT Dispersion

Increased QTd on the surface ECG has been attributed to increased dispersion of ventricular repolarization. However, recent findings suggest that QTd does not truly measure heterogeneity of repolarization but rather reflects the impact of varying T-loop morphology and the magnitude of interlead variation in projection of the T-wave loop.\textsuperscript{16,34,35} The absence of any meaningful correlation between QTd and the sum of T-wave areas,\textsuperscript{25} together with the relatively modest or absence of correlation between PCA ratio and QTd in this and previous studies,\textsuperscript{14,15,25} additionally suggests that QTd does
not reflect true dispersion of repolarization and that PCA ratio and scalar QTd measurements provide different information on repolarization abnormality. However, despite the lack of association of QTd with true heterogeneity of repolarization, increased QTd has been demonstrated to predict risk in a variety of clinical populations.\textsuperscript{10–12} The prognostic value of increased QTd may reflect an ability to quantify abnormalities of repolarization as distinct from true heterogeneity of repolarization.\textsuperscript{16,34}

In contrast to the gender differences in the PCA ratio, men and women had similar QTd values despite longer durations of repolarization and lower T-wave areas in women.\textsuperscript{1,33} This reproduces findings in healthy subjects\textsuperscript{25} and suggests a possible explanation for the gender differences in performance of QTd in the present study. It is intriguing to speculate that this might reflect the method used to determine T-wave offset in the present study, which is dependent on identification of the maximal slope of the descending limb of the T wave,\textsuperscript{20,21} in light of recent observations that the absolute slope of each limb of the T-wave is steeper in men than in women.\textsuperscript{33} The greater descending slope in men could possibly counteract the greater T-wave amplitude in men than in women,\textsuperscript{1,33} producing similar QT interval durations in men and women using this computerized approach, despite clear gender differences in other measures of repolarization heterogeneity.\textsuperscript{1,25,33}

**Methodological Issues**

Accurate and reproducible measurement of QTd has been limited by difficulties with reliable identification of T-wave offset.\textsuperscript{16,20,21} Identification of T-wave offset using the intersection of a least squares–fitted line around the maximum slope of the T wave with the isoelectric line, as used in the present study, has been found to maximize reproducibility of QTd measurements.\textsuperscript{20,21} However, overall reproducibility of the PCA ratio seems to be superior to that of scalar QTd variables,\textsuperscript{20,21} reflecting relative independence of analysis of the spatial T-wave loop from precise determination of T-wave offset. Lower measurement error for the PCA ratio may in part contribute to the improved risk stratification provided by this method. Moreover, exclusion of participants with fewer than 6 total and 3 precordial leads with measurable QT intervals primarily attributable to low-amplitude T-waves\textsuperscript{12} additionally limits utility of QTd. Of note, inclusion of participants who were excluded from analysis on the basis of an inadequate number of QT interval measurements did not significantly change results of the present study with respect to the predictive value of the PCA ratio in men and women. Lastly, exclusion of participants with definite or possible coronary heart disease at baseline did not significantly affect results of these analyses.

**Clinical Implications**

These findings suggest that PCA of the T-wave loop, as performed in the present study, in addition to other novel descriptors of T-wave morphology, can improve stratification of the risk of cardiovascular death by the ECG.\textsuperscript{19} Additional study of these computerized measures of T-wave complexity and their interrelation will be necessary to clarify the role of PCA and other descriptors of T-wave morphology in the prediction of cardiovascular risk in various clinical populations.

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**References**


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