Electrocardiographic Repolarization Complexity and Abnormality Predict All-Cause and Cardiovascular Mortality in Diabetes

The Strong Heart Study

Peter M. Okin,1 Richard B. Devereux,1 Elisa T. Lee,2 James M. Galloway,3 and Barbara V. Howard4

Type 2 diabetes is associated with increased risk of cardiovascular (CV) and all-cause mortality. Although electrocardiographic measures of repolarization abnormality and complexity stratify risk in the general population, their prognostic value in diabetes has not been well characterized. Digital electrocardiogram (ECG) readings were acquired for 994 American Indians with type 2 diabetes. ST segment depression (STD) ≥50 μV and rate-corrected QT interval (QTc) >460 ms were examined as measures of repolarization abnormality. The principal component analysis (PCA) of the ratio of the second to first eigenvalues of the T-wave vector (PCA ratio) (>32.0% in women and >24.6% in men) was examined as a measure of repolarization complexity on the ECG. After a mean follow-up of 4.7 ± 1.0 years, there were 56 CV deaths and 155 deaths from all causes. In univariate analyses, STD, QTc, and the PCA ratio predicted CV and all-cause mortality. After multivariate adjustment for age, sex, and other risk factors, STD (hazard ratio 3.68, 95% CI 1.70–7.96) and PCA ratio (2.61, 1.33–5.13) remained predictive of CV mortality and both STD (2.36, 1.38–4.02) and QTc (2.03, 1.32–3.12) predicted all-cause mortality. Computerized ECG measures of repolarization abnormality and complexity predict CV and all-cause mortality in type 2 diabetes, supporting their use to identify high-risk individuals with diabetes. Diabetes 53:434–440, 2004

The surface electrocardiogram (ECG) remains the most widely used noninvasive method for cardiovascular (CV) risk assessment. Abnormalities of ventricular repolarization on the ECG, such as ST segment depression (STD) and QT interval prolongation, are well-established markers of mortality risk in the general population (1–6). ECG measures of the heterogeneity or complexity of ventricular repolarization have been implicated in the genesis of ventricular arrhythmias and also associated with adverse prognosis (6–14). A number of surface ECG approaches to analysis of repolarization heterogeneity have been proposed, including QT dispersion (6,9,12), T-wave morphology analyses (9,10,13), and principal component analysis (PCA) of the T-wave vector loop (11,14), a spatial measure of T-wave complexity that avoids many of the theoretical and practical limitations of simple QT dispersion and improves prediction of CV death (11,14). However, these repolarization abnormalities may be strongly correlated with one another (11), and whether they provide independent prognostic information when examined together remains unclear.

Diabetes is an established risk factor for CV disease and is associated with an increased risk of both all-cause and CV mortality (15–19). The increasing prevalence of type 2 diabetes, earlier onset of diabetes, and aging of the population will result in an increasing prevalence of diabetes-induced CV disease (18,19), suggesting that accurate noninvasive identification of diabetic individuals at high risk may play a role in the development of more effective preventive strategies for decreasing diabetes-related CV risks (19). Although increased QT interval and QT dispersion have been implicated as possible ECG predictors of CV and all-cause mortality in several small type 2 diabetic cohorts (20–22), the prognostic value of the QT interval has not been examined in an unselected type 2 diabetic population, and the prognostic value of STD and the more accurate PCA ratio have not been assessed in diabetes. Therefore, the present study examined the value of repolarization abnormalities on the ECG, as characterized by STD and a prolonged rate-corrected QT interval (QTc), and repolarization complexity, as measured by the PCA ratio, for prediction of CV and all-cause mortality in adults with diabetes.

RESEARCH DESIGN AND METHODS

Study population. The Strong Heart Study is a community-based study of CV disease and risk factors in American Indians from 13 communities in Arizona, Oklahoma, and North and South Dakota. Detailed information about the population and methods has previously been reported in detail (6,14). Diabetes was diagnosed by World Health Organization criteria (23,24), if fasting blood glucose was >140 mg/dl, 2-h postchallenge glucose was >200 mg/dl, or participants received hypoglycemic medication. These analyses

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CHD, coronary heart disease; CV, cardiovascular; ECG, electrocardiogram; PCA, principal component analysis; QTc, rate-corrected QT interval; STD, ST segment depression.

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**RESULTS**

**Patient characteristics.** After a maximum follow-up of 5 years (mean 4.7 ± 1.0), there were 155 deaths from all causes and 56 CV deaths. Clinical characteristics of survivors, individuals who died from any cause, and participants with and without CV death are compared in Table 1. The 155 participants who died were older and had higher BMIs, lower diastolic blood pressures, more albuminuria, and a greater prevalence of CHD, but did not differ with respect to sex, systolic blood pressure, fasting glucose, GHB, HDL and LDL cholesterol, and serum triglyceride levels, or smoking history compared with individuals who survived. The 56 participants who suffered CV death were similarly older and had higher systolic blood pressures, higher fasting glucose, lower HDL and higher LDL cholesterol levels, more albuminuria, and a greater prevalence of CHD, but did not differ with respect to sex, BMI, GHB or triglyceride levels, diastolic blood pressure, or smoking history from participants who did not die from a CV cause.

The relation of the magnitude of STD, PCA ratio, and QTc interval to clinical outcome is also shown in Table 1. Participants who died of all-cause or CV etiologies had significantly greater STD, higher PCA ratios, and longer QTc intervals than those who survived. Of note, there were no significant differences in mean GHB or fasting glucose levels between participants with and without abnormal STD, an abnormal PCA ratio, or a prolonged QT interval.

**Prediction of all-cause mortality.** In Cox analyses adjusting for possible differences between centers, STD ≥50 μV, QTc >460 ms, and a sex-specific increase in PCA ratio were each individually significant predictors of all-cause mortality (Table 2 and Fig. 2). The 62 participants with STD ≥50 μV had a 4.68-fold increased risk of death, with an actuarial 5-year mortality of 46.8% versus only 13.5% in those with STD <50 μV. The 146 participants with a QTc interval >460 ms had a 1.95-fold increased risk of death and a 5-year mortality of 25.3% compared with 13.9% in individuals with shorter QTc intervals. A PCA ratio >32.0% in women or >24.0% in men (n = 139) was associated with a 2.11-fold increased risk of death and an actuarial 5-year...
TABLE 1
Clinical characteristics, PCA ratio, QTc, and STD measurements in participants according to survival status

<table>
<thead>
<tr>
<th></th>
<th>Survivors</th>
<th>All-cause death</th>
<th>(P)</th>
<th>Survivors and non-CVD death</th>
<th>CVD death</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n)</td>
<td>839</td>
<td>155</td>
<td>—</td>
<td>938</td>
<td>56</td>
<td>—</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56 ± 8</td>
<td>60 ± 9</td>
<td>&lt;0.001</td>
<td>57 ± 8</td>
<td>61 ± 9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>62.9</td>
<td>56.1</td>
<td>0.131</td>
<td>62.6</td>
<td>50.0</td>
<td>0.082</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>32.4 ± 6.1</td>
<td>30.1 ± 6.2</td>
<td>&lt;0.001</td>
<td>32.2 ± 6.2</td>
<td>30.7 ± 5.4</td>
<td>0.154</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>78 ± 10</td>
<td>76 ± 12</td>
<td>0.009</td>
<td>78 ± 10</td>
<td>79 ± 11</td>
<td>0.953</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>131 ± 19</td>
<td>133 ± 25</td>
<td>0.153</td>
<td>131 ± 19</td>
<td>137 ± 27</td>
<td>0.035</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>11.5 ± 4.5</td>
<td>11.7 ± 5.1</td>
<td>0.070</td>
<td>11.5 ± 4.6</td>
<td>12.0 ± 4.4</td>
<td>0.012</td>
</tr>
<tr>
<td>GHb (%)</td>
<td>8.76 ± 2.51</td>
<td>8.35 ± 2.43</td>
<td>0.235</td>
<td>8.73 ± 2.52</td>
<td>9.12 ± 1.76</td>
<td>0.776</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.09 ± 0.28</td>
<td>1.11 ± 0.34</td>
<td>0.992</td>
<td>1.09 ± 0.28</td>
<td>0.93 ± 0.21</td>
<td>0.002</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>2.90 ± 0.80</td>
<td>2.82 ± 1.14</td>
<td>0.520</td>
<td>2.87 ± 0.83</td>
<td>3.23 ± 1.29</td>
<td>0.004</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>178 ± 165</td>
<td>187 ± 193</td>
<td>0.668</td>
<td>177 ± 162</td>
<td>219 ± 263</td>
<td>0.033</td>
</tr>
<tr>
<td>Albuminuria (log mg/g)</td>
<td>3.73 ± 2.15</td>
<td>5.00 ± 2.44</td>
<td>&lt;0.001</td>
<td>3.84 ± 2.21</td>
<td>5.03 ± 2.48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prevalent CHD (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td>None</td>
<td>77.7</td>
<td>58.1</td>
<td></td>
<td>75.7</td>
<td>57.1</td>
<td></td>
</tr>
<tr>
<td>Possible</td>
<td>19.0</td>
<td>31.6</td>
<td></td>
<td>20.3</td>
<td>32.1</td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>3.3</td>
<td>10.3</td>
<td></td>
<td>4.1</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.600</td>
</tr>
<tr>
<td>Never</td>
<td>32.5</td>
<td>34.8</td>
<td>0.832</td>
<td>33.3</td>
<td>26.8</td>
<td></td>
</tr>
<tr>
<td>Previous</td>
<td>40.9</td>
<td>37.4</td>
<td></td>
<td>40.4</td>
<td>39.3</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>26.6</td>
<td>27.7</td>
<td></td>
<td>26.3</td>
<td>33.9</td>
<td></td>
</tr>
<tr>
<td>STD ((\mu V))</td>
<td>-14.4 ± 19.6</td>
<td>-25.3 ± 28.2</td>
<td>&lt;0.001</td>
<td>-15.1 ± 20.5</td>
<td>-31.3 ± 30.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>435 ± 24</td>
<td>444 ± 30</td>
<td>&lt;0.001</td>
<td>436 ± 25</td>
<td>442 ± 32</td>
<td>0.028</td>
</tr>
<tr>
<td>PCA ratio (%)</td>
<td>18.7 ± 12.2</td>
<td>22.5 ± 14.8</td>
<td>&lt;0.001</td>
<td>19.0 ± 12.5</td>
<td>24.2 ± 15.2</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data are means ± SD unless otherwise indicated. CVD, cardiovascular disease.

mortality of 26.6 versus 13.8% in individuals with lower PCA ratios.

In additional Cox models that considered all three measures of repolarization with adjustment for age, BMI, diastolic and systolic blood pressures, HDL and LDL cholesterol, triglycerides, albuminuria, alcohol use, prevalent CHD, history of smoking, and study center, both abnormal STD and an increased QTc interval remained significant independent predictors of all-cause mortality (Table 2). However, an increased PCA ratio did not significantly predict all-cause mortality independent of clinical covariates and other repolarization measures. The predictive value of these ECG variables was similar in participants with and without prevalent CHD (Table 2). Of note, STD and QTc, but not the PCA ratio, remained significant predictors of all-cause mortality when entered as continuous variables in the Cox models.

**Prediction of CV mortality.** In Cox analyses that adjusted for center, STD ≥50 \(\mu V\), QTc >460 ms, and a PCA ratio above sex-specific partition values were significant univariate predictors of CV mortality (Table 3 and Fig. 3). STD ≥50 \(\mu V\) was associated with a 9.54-fold increased risk of CV death, with an actuarial 5-year CV mortality of 33.4% versus only 4.3% in individuals with STD <50 \(\mu V\). A prolonged QTc interval was associated with a 2.07-fold increased risk of CV death and with a 5-year CV mortality of 10.4% compared with 5.2% in individuals with shorter QTc intervals. An increased PCA ratio was associated with

TABLE 2
Cox proportional hazards models for prediction of all-cause mortality

<table>
<thead>
<tr>
<th></th>
<th>Total population ((n = 994))</th>
<th>No CHD ((n = 742))</th>
<th>Possible or definite CHD ((n = 252))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(HR) 95% CI (\chi^2) (P)</td>
<td>(HR) 95% CI (\chi^2) (P)</td>
<td>(HR) 95% CI (\chi^2) (P)</td>
</tr>
<tr>
<td>Adjusted for center only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STD ≥50 (\mu V)</td>
<td>4.68 3.12–7.01 55.9 0.001</td>
<td>5.08 2.46–10.51 19.2 &lt;0.001</td>
<td>2.98 1.77–5.02 16.9 &lt;0.001</td>
</tr>
<tr>
<td>PCA ratio*</td>
<td>2.11 1.46–3.05 15.7 0.001</td>
<td>1.44 0.77–2.70 1.3 0.259</td>
<td>1.88 1.15–3.09 6.2 0.013</td>
</tr>
<tr>
<td>QTc &gt;460 ms</td>
<td>1.95 1.35–2.83 12.6 0.001</td>
<td>1.90 1.16–3.12 6.4 0.011</td>
<td>1.82 1.05–3.17 4.5 0.033</td>
</tr>
<tr>
<td>Adjusted for multiple covariates†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STD ≥50 (\mu V)</td>
<td>2.36 1.38–4.02 9.8 0.002</td>
<td>2.87 1.05–1.12 4.2 0.040</td>
<td>1.95 1.01–3.76 3.9 0.047</td>
</tr>
<tr>
<td>PCA ratio*</td>
<td>1.33 0.82–2.13 1.3 0.246</td>
<td>1.08 0.49–2.38 0.1 0.848</td>
<td>1.44 0.80–2.59 1.5 0.221</td>
</tr>
<tr>
<td>QTc &gt;460 ms</td>
<td>2.03 1.32–3.13 10.4 0.001</td>
<td>2.19 1.25–3.81 7.6 0.043</td>
<td>1.43 0.74–2.78 1.1 0.287</td>
</tr>
</tbody>
</table>

*≥32.0% in women, >24.6% in men. †Cox model with all three ECG variables entered, adjusted for age, BMI, diastolic and systolic blood pressures, fasting glucose, GHb, HDL and LDL cholesterol levels, triglyceride level, albuminuria, alcohol use, history of smoking, and study center. Prevalent CHD was included as a covariate only in the total population. HR, hazard ratio.
a 3.17-fold greater risk of CV death and with an actuarial 5-year CV mortality of 13.8% versus only 4.7% in individuals with lower PCA ratios.

Multivariate Cox analyses (Table 3) demonstrated that after adjustment for other potential predictors of CV mortality, both abnormal STD and an increased PCA ratio remained in the Cox model as significant predictors of CV mortality. In contrast, a prolonged QTc interval was no longer a significant predictor of CV mortality in multivariate analyses. Risk stratification for CV mortality was similar in subgroups of the population with and without CHD (Table 3). STD and the PCA ratio, but not the QTc interval, were both significant predictors of CV mortality in multivariate analyses when considered as continuous as opposed to discrete variables. Of note, exclusion of participants who suffered a non-CV death from the Cox analyses did not affect the predictive value of these ECG variables for CV mortality.

**DISCUSSION**

In a large population-based prospective study of American Indians with type 2 diabetes, computerized ECG measurement of abnormalities and heterogeneity of ventricular repolarization predicted both all-cause and CV mortality. After adjustment for other known predictors of adverse outcome, computerized measurements of STD and QTc, which quantify degree of repolarization abnormality, remained associated with all-cause mortality. In addition, both STD and the PCA ratio, an ECG measure of repolarization or T-wave complexity, remained significant predictors of CV mortality. These findings support the value of these computerized ECG methods for noninvasive risk stratification in adults with diabetes.

**ECG abnormalities and prognosis in diabetes.** Previous studies of the predictive value of repolarization changes on the resting ECG in type 2 diabetic patients have been limited to examining QT interval prolongation and dispersion in small cohorts of patients (20–22). In 182 patients with newly diagnosed type 2 diabetes enrolled in the Dundee cohort of the U.K. Prospective Diabetes Study and followed for a mean of 10.3 years (20), both QT dispersion and maximal QTc interval were significant predictors of cardiac death in multivariate Cox analyses. However, no data were presented on the actual mortality rate in the population or on the prevalence of abnormal QT interval or dispersion findings. Sawicki et al. (21) similarly demonstrated that greater QT dispersion was an independent predictor of all-cause, CV, and cerebrovascular mortality in a tertiary care center–based cohort of 216 diabetic patients with a 73% mortality over a maximum follow-up period of 16 years. Christensen et al. (22) found high prevalences of a QTc/H11022 440 ms1/2 (67%) and of QT dispersion/H11022 50 ms (51%) in a cohort study of 324 patients with type 2 diabetes and that prolonged QTc, but not QT dispersion, was an independent predictor of all-cause and CV mortality. However, the value of QT dispersion for risk stratification has been limited by difficulties with accurate and reproducible manual measurements, by the resultant need to exclude leads with low T-wave amplitudes from analyses, and by the failure of QT dispersion to independently predict CV mortality in men (6,9,14,25,26).

The present findings demonstrate the value of a prolonged QT interval for predicting all-cause but not CV mortality and the predictive value of increased T-wave complexity, as measured by the PCA ratio, for CV but not all-cause mortality in a population with type 2 diabetes. These results mirror similar findings for both QTc and the PCA ratio in the overall Strong Heart Study population (6,14). Importantly and in contrast to QT dispersion, the PCA ratio stratifies risk of CV mortality in both men and women (14), and overall reproducibility of the PCA ratio appears to exceed significantly that of QT dispersion variables (25,26), perhaps contributing to the improved
risk stratification offered by this method (14). The present study further demonstrates the strong prognostic value of minor degrees of STD for both CV and all-cause mortality in diabetes, paralleling similar minor degrees of STD for both CV and all-cause mortality study further demonstrates the strong prognostic value of risk stratifications in diabetes, including left ventricular hypertrophy (3,34), and the elevated risk of ventricular arrhythmias associated with increased complexity of repolarization (6,14). The ability of STD and an increased QTc to predict all-cause mortality is less readily explained. It is possible that an increased QTc may be related to underlying disorders associated with diabetes, including diabetic renal dysfunction, which are in turn associated with an increased risk of early death and electrolyte abnormalities and/or medications that may cause QT prolongation (6,22). On the other hand, QT prolongation might also reflect profound alterations in neurohormonal balance that could predispose to an increased risk of mortality (6,22). The association of STD with all-cause mortality could be a further reflection of the strong association between STD and left ventricular hypertrophy (34) and the known relationship of hypertrophy to all-cause mortality (35). In addition, the negative prognostic impact of these ECG findings could be mediated via the adverse effects of diabetes on CV function, including reduced left ventricular systolic function, increased arterial stiffness, and abnormal relaxation (24,36). Further study of the relation between these ECG findings and cardiac structure and function in type 2 diabetes may provide greater insight into these putative mechanisms.

**Ventricular repolarization and diabetes.** Beyond the possible relation of alterations in ventricular repolarization to underlying CV structural and functional abnormalities in type 2 diabetes (3,34–36), abnormalities of ventricular repolarization in diabetes may also reflect direct effects of diabetes perse on the electrophysiology of ventricular myocardium (37,38). In experimental diabetic rat heart, the most prominent electrophysiological alteration is an increase in action potential duration (37) with a resultant prolongation of the QT interval. Mechanistically, this may reflect changes in voltage-gated K⁺ channel gene expression because of isoform switching from Kv4.2 to Kv4.1 with attendant slower kinetics of transient outward K⁺ currents (37). In addition, prolongation of ventricular action potential duration may alter the normal endocardial-epicardial action potential gradient, producing ST segment and T-wave changes on the ECG (38). These alterations could potentially produce an increase in re-entrant arrhythmias, particularly in association with abrupt changes in cycle length, when rate-dependent changes in action potential duration can be expected to occur (39). It is important to note, however, that the cardiac electrophysiological behavior of rat models of diabetes may not be directly transferable to humans because of possible differences in the α subunits that underlie these currents in the two species (37,38). Unfortunately, there are no large animal or guinea pig models of altered QT interval behavior in diabetes that might more closely resemble human electrophysiological behavior.

### Methodological issues and study limitations
This study and previous investigations are affected by fundamental limitations in the accuracy and reproducibility QT interval measurements because of difficulties with reliable detection of T-wave offset (9,14,25,26). However, the computerized method used to determine T-wave offset in the current study has greater reproducibility than manual measurements or other computer-based methods (25,26). The absence of serial ECG data prevents assessment of the predictive value of incident repolarization abnormalities and suggests that the present findings may reflect a somewhat conservative estimate of the true prognostic value of these ECG findings, since it is likely that some proportion of participants will develop new repolarization abnormalities over time. Although follow-up was truncated at 5 years in the current analyses to limit the impact of possible subsequent changes in repolarization on outcome, further study will be necessary to determine the
prognostic value of serial changes in ECG repolarization. Moreover, the absence of information on the use of medications that could effect repolarization is a potential limitation of the current study. Lastly, although a relationship between these ECG abnormalities and CV mortality may be more readily appreciated than one with non-CV death, categorization of cause of death in any study can be difficult (40). Thus, all-cause mortality was used as an additional end point that obviates any potential error associated with misclassification of cause of death.

Clinical implications. These findings suggest quantita-
tive assessment of the degree of repolarization abnormal-
node, and complexity on the surface ECG can provide
independent risk stratification in adults with type 2 diabe-
tes. This study expands on the value of determination of
the maximal QTc interval found in previous small cohorts
with diabetes for the assessment of all-cause mortality risk
(20–22) and demonstrates the additive value of simple
computerized measurement of the magnitude of STD for
prediction of overall mortality risk in diabetes. Moreover,
we demonstrate that STD and PCA of the T-wave loop, a
more accurate measure of T-wave complexity or hetero-
genosity than QT dispersion (13,14), provide additional
prognostic information for CV mortality in diabetic sub-
jects. For the clinician, it is important to point out that
STD, the QTc interval, and PCA ratio can readily be
adapted into the standard use and interpretation of the
ECG given the widespread and growing use of digital ECG
equipment. Further study will be necessary to establish
whether more aggressive treatment of diabetes and/or the
CV manifestations of diabetes can reduce mortality in
adults with type 2 diabetes and these ECG markers of
increased risk and whether the predictive value of these
ECG variables can be extended to type 1 diabetes.

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York.

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