Combined Echocardiographic Left Ventricular Hypertrophy and Electrocardiographic ST Depression Improve Prediction of Mortality in American Indians

The Strong Heart Study

Peter M. Okin, Mary J. Roman, Elisa T. Lee, James M. Galloway, Barbara V. Howard, Richard B. Devereux

Abstract—Echocardiographic left ventricular hypertrophy (Echo-LVH) and ST segment depression (STD) on the ECG have each been demonstrated to predict cardiovascular (CV) and all-cause (AC) mortality. However, the prognostic value of combining Echo-LVH and ECG-STD has not been examined. ECGs and echocardiograms were examined in 2193 American Indian participants in the second Strong Heart Study examination. STD was measured by computer and was considered abnormal if ≥50 µV. Echo-LVH was defined by indexed LV mass >116 g/m² in men and >104 g/m² in women. After a mean follow-up of 3.1±0.7 years, there were 57 CV and 169 AC deaths. In univariate Cox analyses, Echo-LVH (χ²=54.2 and χ²=68.5) and ECG-STD (χ²=35.9 and χ²=46.3, all P<0.001) predicted CV and AC mortality, respectively. The combination of Echo-LVH and ECG-STD improved risk stratification compared with either alone for both CV death (χ²=74.4, P<0.001) and AC death (χ²=102.0, P<0.001), with presence of both ECG-STD and Echo-LVH associated with the greatest risks. After adjustment for age, sex, and relevant risk factors, combined Echo-LVH and ECG-STD remained predictive of CV mortality (χ²=19.7, P<0.001) and AC mortality (χ²=24.9, P<0.001), with the presence of both Echo-LVH and ECG-STD associated with a 6.3-fold increased risk of CV death (95% CI: 2.8 to 14.2) and a 4.6-fold increased risk of AC mortality (95% CI: 2.5 to 8.5). ECG-STD and Echo-LVH additively increase the risk of both CV mortality and AC mortality. These findings support the value of combining Echo-LVH and ECG-STD to improve risk stratification. These findings require verification in other populations. (Hypertension. 2004;43:769-774.)

Key Words: electrocardiography ■ hypertrophy ■ echocardiography ■ mortality

The standard resting ECG remains the most widely used noninvasive tool for assessing risk in population-based studies and in clinical practice. Left ventricular hypertrophy (LVH) on the 12-lead ECG is and detected by echocardiography are common manifestations of cardiovascular disease (CVD) that strongly predict CVD and all-cause mortality. Indeed, increased LV mass index and ECG LVH as defined by Cornell voltage-duration product criteria appear to predict all-cause mortality independently of each other in elderly men. However, limited sensitivity of standard ECG voltage criteria for LVH has decreased usefulness of the ECG for detecting patients with anatomic hypertrophy and for screening subjects considered at high risk, despite the greater availability and lower cost of the ECG compared with echocardiography.

ST segment depression (STD) on the ECG, a marker of ventricular repolarization abnormality, is a well established marker of risk in the general population that is also strongly associated with underlying CVD, including LVH. The classic strain pattern on the ECG of STD and T-wave inversion in the lateral precordial leads is a well recognized marker of anatomic LVH, which has been the strongest predictor of increased morbidity and mortality when ECG LVH criteria have been used for risk assessment. Recently, we demonstrated that even minimal computer-measured STD in lateral precordial leads is associated with higher LV mass and greater prevalence of anatomic LVH. The strong relation of STD to increased LV mass raises the unanswered question of whether computer-measured STD and Echo-LVH are related to CVD events by the same

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pathway, or whether they provide independent prognostic information. Thus, the present study examined whether Echo-LVH and ECG STD have additive predictive value for CVD and all-cause mortality while controlling for clinical and demographic variables that could potentially confound these relationships.

Methods

Study Population
The Strong Heart Study is a population-based study of CVD and its risk factors in American Indians from 13 communities in Arizona, Oklahoma, and North and South Dakota. Detailed information about the population, methods, and enrollment procedures for the study have been previously reported in detail. The current study examined 2193 participants in the second Strong Heart Study examination (64% female, mean age 59±8 years) with digital ECG records in sinus rhythm with no bundle branch block.

Electrocardiography
Standard 12-lead ECGs were performed with MAC-PC or MAC-12 digital ECG systems (GE Medical Systems) as previously described. Absolute ST segment deviation was measured by computer with 5 μV precision at the midpoint of the ST segment; this measurement has 100% reproducibility when applied to the same digital ECG. STD ≥50 μV in any lead (excluding aVR) was considered abnormal, a value that corresponds to the 95th percentile of STD findings and that stratifies mortality risk in participants in the first Strong Heart Study examination.

Echocardiography
Studies were performed using fundamental imaging with commercially available phased-array echocardiographs as previously described. LV mass was calculated and was indexed for body surface area. Repeat LV mass measurements by these methods are highly reproducible, with an intraclass correlation coefficient of 0.93. LVH was considered present if LV mass index was >104 g/m² in women or >116 g/m² in men.

Determination of Endpoints
Deaths were identified and verified and were classified as CVD if caused by myocardial infarction, stroke, sudden death from coronary heart disease, or congestive heart failure as previously reported.

Data and Statistical Analyses
Data were analyzed with SPSS release 10.0 (SPSS Inc.). Data are presented as mean±SD for continuous variables and as proportions for categorical variables. Mean values were compared between groups using 2-way ANOVA to adjust for possible gender differences. Proportions were compared by χ² tests. Mortality rates were calculated and plotted by the Kaplan-Meier product-limit method; death rates were compared between groups with the log-rank test. Mortality analyses were performed by fitting Cox proportional hazards models to the data with stratification by center. The estimated relative hazard (HR) of death associated with positive test outcomes was computed as the anti-log of the estimated coefficient for dichotomous variables. The 95% CI of each relative risk was calculated from the estimated coefficients and their standard errors, and Wald χ² statistics and probability values were calculated. To test the independence of STD and Echo-LVH as predictors of mortality, both variables were entered together into forward stepwise multivariate Cox models that included as covariates significant univariate Cox predictors of CVD or all-cause mortality. To test the complimentary information provided by Echo-LVH and STD criteria, a combined test criterion was derived that incorporated both measures into 3 categories: both STD and Echo-LVH negative, either STD or Echo-LVH positive, and both STD and Echo-LVH positive. For all tests, a 2-tailed P<0.05 was considered significant.

Results

Patient Characteristics
After a mean follow-up of 3.1±0.7 years, there were 169 deaths from all causes and 57 CVD deaths. Compared with those who survived, the 169 participants who died were older and had lower body mass indexes, higher systolic and lower diastolic blood pressures, lower LDL cholesterol and higher fasting glucose levels, greater albuminuria, and higher prevalences of coronary heart disease, diabetes, and hypertension; however, they did not differ with respect to gender, HDL cholesterol or triglyceride levels, or smoking history compared with those who survived. The 57 participants who had CVD death were similarly older and had higher systolic blood pressures, lower HDL levels, more albuminuria, and greater prevalences of coronary heart disease, diabetes, and hypertension; however, they did not differ with respect to gender, body mass index, diastolic pressure, LDL cholesterol or triglyceride levels, fasting glucose, or smoking history from participants who did not die from a CVD cause.

The magnitudes of STD, LV mass, and indexed LV mass are also shown in relation to clinical outcomes in Table 1. Participants who died of both all-cause and CVD factors had significantly greater STD, higher LV mass, and greater indexed LV mass than those who survived.

Prediction of Cardiovascular and All-Cause Mortality
In Cox analyses stratified for study center, ECG-STD and Echo-LVH were each significant predictors of CVD and all-cause mortality (Table 2, Figures 1 and 2). STD ≥50 μV was present in 133 participants (6.1%) and was associated with a 26-fold increased risk of CVD death and with a nearly 4-fold increased risk of all-cause mortality, with actuarial 3-year CVD mortality of 10.0% and all-cause mortality of 20.2% compared with 1.9% and 6.0%, respectively, in those with STD <50 μV (each P<0.0001). Echo-LVH was present in 209 participants (9.5%) and was associated with greater than 7-fold increased risk of CVD death and with a 4-fold higher risk of death from any cause, with 3-year CVD mortality of 10.7% and total mortality of 18.6% compared with 3-year CVD and all-cause mortality of 1.5% and 5.7%, respectively, in those without hypertrophy (each P<0.0001).

After adjustment for the possible predictive value of age, gender, body mass index, diastolic and systolic blood pressures, HDL and LDL cholesterol, triglyceride and fasting glucose levels, albuminuria, alcohol use, diabetes, and history of smoking or prevalent coronary heart disease, both STD ≥50 μV and Echo-LVH remained in the Cox models as significant predictors of CVD and all-cause mortality, as did age and albuminuria (Table 2). Importantly, considering STD and LV mass index as continuous variables preserved their independent predictive value for CVD (HR=1.38; 95% CI: 1.14 to 1.68 per 25 μV of STD; and HR=1.49; 95% CI: 1.17 to 1.91 per 25 g/m² of LV mass index) and all-cause mortality (HR=1.28; 95% CI: 1.11 to 1.49; and HR=1.53; 95% CI: 1.26 to 1.86) in multivariate analyses.
when either variable was abnormal, and 5.5% when both tests were abnormal (P<0.001). Multivariate Cox analyses (Table 3) demonstrated that after adjustment for other potential predictors of mortality, the combination of ECG-STD and Echo-LVH remained a significant predictor of CVD and all-cause mortality along with age and albuminuria, with the presence of ECG-STD and Echo-LVH associated with a 6.3-fold increased risk of CVD death and a 4.6-fold increased risk of all-cause mortality after adjusting for covariates.

**Discussion**

This study demonstrates that the combination of ST depression on the ECG and increased LV mass by echocardiogram dramatically increases the risk of CVD and all-cause mortality. ECG-STD and increased LV mass provide additive prognostic information, independently of each other and of other risk factors known to predict mortality. The absence of

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**TABLE 1. Clinical Characteristics, ST Segment Depression, and Echocardiographic Left Ventricular Mass Measurements in Participants According to Survival Status**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors (n=2024)</th>
<th>All-Cause Death (n=169)</th>
<th>P Value</th>
<th>Survivors and Non-CVD Death (n=2136)</th>
<th>CVD Death (n=57)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>59±8</td>
<td>63±9</td>
<td>&lt;0.001</td>
<td>59±8</td>
<td>64±8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>64.5</td>
<td>58.0</td>
<td>0.106</td>
<td>64.0</td>
<td>63.2</td>
<td>1.000</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>31.0±6.1</td>
<td>29.6±5.8</td>
<td>0.010</td>
<td>30.9±6.1</td>
<td>30.3±5.5</td>
<td>0.517</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>129±20</td>
<td>134±23</td>
<td>0.001</td>
<td>129±20</td>
<td>139±22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>75±10</td>
<td>73±12</td>
<td>0.055</td>
<td>75±10</td>
<td>75±12</td>
<td>0.319</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>42±14</td>
<td>41±13</td>
<td>0.781</td>
<td>42±14</td>
<td>38±12</td>
<td>0.057</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>120±34</td>
<td>113±41</td>
<td>0.022</td>
<td>120±35</td>
<td>122±38</td>
<td>0.401</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>157±112</td>
<td>158±143</td>
<td>0.821</td>
<td>156±115</td>
<td>168±107</td>
<td>0.632</td>
</tr>
<tr>
<td>Albuminuria (log mg/g)</td>
<td>3.16±1.92</td>
<td>4.71±2.60</td>
<td>&lt;0.001</td>
<td>3.22±1.97</td>
<td>5.31±2.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>154±80</td>
<td>167±85</td>
<td>&lt;0.001</td>
<td>154±80</td>
<td>167±81</td>
<td>0.166</td>
</tr>
<tr>
<td>Prevalent CHD (%)</td>
<td>3.9</td>
<td>10.7</td>
<td>&lt;0.001</td>
<td>4.1</td>
<td>17.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (% current)</td>
<td>32.5</td>
<td>32.5</td>
<td>1.000</td>
<td>32.5</td>
<td>33.3</td>
<td>1.000</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>46.1</td>
<td>64.7</td>
<td>&lt;0.001</td>
<td>46.7</td>
<td>78.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of Hypertension (%)</td>
<td>42.3</td>
<td>56.5</td>
<td>&lt;0.001</td>
<td>42.6</td>
<td>73.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ST depression (µV)</td>
<td>−16.1±20.5</td>
<td>−28.7±31.4</td>
<td>&lt;0.001</td>
<td>−16.5±20.8</td>
<td>−38.8±40.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>156±38</td>
<td>179±50</td>
<td>&lt;0.001</td>
<td>157±39</td>
<td>191±56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>83±18</td>
<td>97±27</td>
<td>&lt;0.001</td>
<td>83±19</td>
<td>105±31</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Combined Echocardiographic LVH and ECG ST Depression Criteria**

Because Echo-LVH and STD criteria provided independent prognostic information, the ability of the combination of these variables to stratify mortality risk was assessed (Table 3 and Figure 3). In Cox analyses stratified by study center, the combined Echo-LVH and ECG STD variable improved risk stratification compared with either Echo-LVH or STD alone for CVD and all-cause mortality, with the presence of ECG-STD and Echo-LVH associated with the greatest risks. Three-year CVD mortality was 20.4% in participants with STD ≥50 µV and Echo-LVH, 6.5% in those with either ECG-STD or Echo-LVH, and only 1.4% in those in whom both variables were negative (P<0.001). Three-year mortality from all causes was 35.7% in the presence of ECG-STD and Echo-LVH, 12.0% when either variable was abnormal, and 5.5% when both tests were negative (P<0.001).

**TABLE 2. Cox Proportional Hazards Models of ST Segment Depression and Echocardiographic Left Ventricular Hypertrophy for Prediction of All-Cause and Cardiovascular Mortality**

<table>
<thead>
<tr>
<th>Variable</th>
<th>All-Cause Mortality</th>
<th>Cardiovascular Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Univariate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST depression ≥50 µV</td>
<td>3.87</td>
<td>2.62–5.72</td>
</tr>
<tr>
<td>Echo-LVH</td>
<td>4.08</td>
<td>2.92–5.68</td>
</tr>
</tbody>
</table>

**Multivariate***

| ST depression ≥50 µV            | 2.04        | 1.24–3.36 | 7.9  | 0.005   | 2.12        | 1.03–4.40   | 4.1  | 0.043   |
| Echo-LVH                        | 1.79        | 1.17–2.74 | 7.1  | 0.008   | 2.35        | 1.21–4.56   | 6.4  | 0.012   |

*Echo indicates echocardiographic; LVH, left ventricular hypertrophy.

Including both ST segment depression ≥50 µV and echocardiographic LVH in the model and adjusted for the possible effects of age, body mass index, diastolic and systolic blood pressures, HDL and LDL cholesterol levels, triglyceride level, fasting glucose, albuminuria, prevalent coronary heart disease, diabetes, alcohol use, and history of smoking, stratified by study center.
Echo-LVH and ECG-STD identifies a large group at relatively low 3-year risk of death, whereas the presence of both abnormalities identifies a subgroup at markedly increased risk of 3-year mortality. These findings support the value of combining simple Echo-LVH and computerized ECG-STD criteria to improve risk stratification.

The separate predictive values of Echo-LVH and ECG-STD for mortality have been well documented in a range of populations, with convincing evidence for a continuous relationship between increasing LV mass and risk. Although ECG voltage criteria for LVH have limited accuracy for detecting anatomic LVH and limited prognostic value when examined alone, previous ECG studies found that the marked lateral repolarization abnormalities of the strain pattern were strong predictors of adverse outcome. However, the strain pattern is uncommon in the absence of significant hypertension and a high prevalence of anatomic LVH, and the fundamental qualitative nature of the strain pattern further limits its usefulness for serial assessment of ECGs and risk stratification. Minor degrees of ECG-STD are more common, even in the absence of true hypertrophy, and are also strongly associated with mortality risk. In addition, there appears to be a continuous relationship between the magnitude of even minor degrees of STD and all-cause and CVD mortality, suggesting that use of quantitative measures of STD can enhance ECG risk stratification.

However, limited data exist on the combination of ECG and echocardiogram for risk stratification, and the value of combining Echo-LVH and ECG-STD has not previously been examined.

In a population-based study of men aged 70, Echo-LVH and Cornell product ECG-LVH predicted mortality independently of each other and of other cardiac risk factors, suggesting that ECG and Echo-LVH provide different prognostic information. Left ventricular strain on the ECG was present in 11.1% of the overall population and was significantly more common in subjects with Echo-LVH (20.8%) and with LVH by Cornell product criteria. However, LV strain did not significantly predict all-cause or CVD mortality in univariate analyses in these elderly men, and STD was not examined as either a discrete or a continuous variable. In the present study, ECG-STD and Echo-LVH had independent predictive value for all-cause and CVD mortality after adjusting for other potential risk factors, and this additive prognostic value was independent of whether LV mass or STD were examined using discrete partition values or as continuous measurements. The combination of both Echo-LVH and ECG-STD conveyed the greatest mortality risks, with hazard ratios of 4.6 for all-cause mortality and 6.3 for CVD mortality after adjusting for other risk factors. Findings were similar when men and women were examined separately and when participants with known or suspected coronary heart disease were excluded.

Figure 1. Kaplan-Meier plots of cumulative cardiovascular mortality (A) and all-cause mortality (B) according to the magnitude of STD partitioned at 50 μV.

Figure 2. Kaplan-Meier plots of cumulative cardiovascular mortality (A) and all-cause mortality (B) according to the presence or absence of echocardiographic LVH defined by indexed left ventricular mass >104 g/m² in women or >116 g/m² in men.
were excluded from analyses. In light of the recent finding that the combination of microalbuminuria and ST segment/T-wave abnormalities on the ECG defined by Minnesota codes 4.1 to 4 and 5.1 to 4 also greatly increased the risk of CVD and all-cause mortality, it should be noted that the predictive value of the combination of Echo-LVH and ECG-STD in multivariate models in the present study was independent of the impact of microalbuminuria on outcomes (Tables 2 and 3). The finding that only albuminuria and age provided additional prognostic information in the multivariate models beyond that provided by the combined Echo-LVH and ECG-STD variable does not diminish the value of traditional risk factors such as diabetes, smoking, cholesterol, or history of coronary disease. Rather, this finding suggests that albuminuria and the combined Echo-LVH and ECG-STD variable may integrate the predictive power of traditional risk factors. In contrast to the findings of Sundström et al, Cornell product criteria for LVH did not enter the Cox models for prediction of either all-cause or CVD mortality in the current study once both Echo-LVH and ECG-STD were in the models, suggesting that STD criteria provide greater additional prognostic information than voltage-duration product criteria once echocardiographic LV mass is taken into account.

Several potential limitations should be considered with respect to these findings. First, it is unclear to what degree these findings in American Indians can be extrapolated to other ethnic populations. However, the demonstrated predictive value of Echo-LVH and minor degrees of STD in other populations when examined separately from each other suggests that the combination of Echo-LVH and ECG-STD will stratify risk in other populations as well. Second, the absence of serial echocardiograms and ECGs precludes analysis of the impact of changes in STD and/or LV mass on risk. The demonstrated relationship of changes in echocardiographic LV mass and the strain pattern on the ECG to outcome suggest that the present findings may underestimate the true prognostic value of STD and LV mass, because it is likely that a proportion of participants will have new or worsening repolarization abnormalities and/or increasing LV mass over time. Last, both the availability and accuracy of computerized ST measurements are important issues with
respect to these findings, and their use may be viewed as a strength and a potential limitation of the present study. Although these computerized ST measurements are not widely used in clinical practice, they are readily accessible on almost all standard digital ECG machines in use today. Perhaps more importantly, we have previously demonstrated that precise visual measurements of ST depression closely replicate computer assessment of ST depression in the assignment of Minnesota ST codes\textsuperscript{12} and accurately reflect the absolute magnitude of ST depression, even during exercise testing.\textsuperscript{22}

Perspectives

The major implication of this study for clinicians is the value of the echocardiogram and ECG in the assessment of risk, suggesting the use of both noninvasive modalities in routine clinical assessment of patients at risk. The present study taken together with previous observations that regression of the typical strain pattern on the ECG appears to be associated with improved prognosis\textsuperscript{2} and with decreases in LV mass,\textsuperscript{23} provide further impetus for evaluation of serial changes in STD for additional refinement of risk stratification by the ECG. Although the present study did not show a significant prognostic role for Cornell voltage-duration product criteria once echocardiographic LV mass was known, recent findings demonstrating that serial assessment of Cornell product criteria can identify hypertensive patients who benefit most from antihypertensive therapy\textsuperscript{3} suggest that it may be efficacious and cost-effective to use these more accurate ECG LVH criteria in hypertensive patients in conjunction with STD findings. However, further study will be necessary to determine the relative role of newer ECG LVH criteria versus Echo-LVH in risk assessment in higher-risk populations. At the present time, both Echo-LVH and ECG-STD should be assessed to provide the greatest prognostic information.

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References

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