Electrocardiographic Strain Pattern and Prediction of Cardiovascular Morbidity and Mortality in Hypertensive Patients

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Abstract—The ECG strain pattern of lateral ST depression and T-wave inversion is a marker for left ventricular hypertrophy (LVH) and adverse prognosis in population studies. However, whether ECG strain is an independent predictor of cardiovascular (CV) morbidity and mortality in the setting of aggressive antihypertensive therapy is unclear. ECGs were examined at study baseline in 8854 hypertensive patients with ECG LVH who were treated in a blinded manner with atenolol- or losartan-based regimens. Strain was defined by the presence of a downsloping convex ST segment with an inverted asymmetrical T wave opposite to the QRS axis in leads V5 and/or V6 and was present in 971 patients (11.0%). The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study composite end point of CV death or nonfatal myocardial infarction or stroke occurred in 1035 patients (11.7%). In Cox analyses adjusting only for treatment effect, ECG strain was a significant predictor of CV death (hazard ratio [HR] 2.26, 95% confidence interval [CI] 1.78 to 2.86), fatal/nonfatal myocardial infarction (HR 2.16, 95% CI 1.67 to 2.80), fatal/nonfatal stroke (HR 1.76, 95% CI 1.39 to 2.21), and the composite CV end point (HR 1.99, 95% CI 1.70 to 2.33). After further adjusting for standard CV risk factors, baseline blood pressure, and severity of ECG LVH, ECG strain remained a significant predictor of CV mortality (HR 1.53, 95% CI 1.18 to 2.00), myocardial infarction (HR 1.55, 95% CI 1.16 to 2.06), and the composite CV end point (HR 1.33, 95% CI 1.11 to 1.59). Thus, ECG strain is a marker of increased CV risk in hypertensive patients in the setting of aggressive blood pressure lowering, independent of baseline severity of ECG LVH. (Hypertension. 2004;44:48-54.)

Key Words: coronary disease ■ electrocardiography ■ hypertension

The classic strain pattern of ST depression and T-wave inversion on the ECG is a well recognized marker of the presence of anatomic left ventricular hypertrophy (LVH), independent of the possible relationship of this repolarization abnormality to underlying coronary heart disease. Indeed, the presence of even minimal degrees of ST depression in the lateral precordial leads is associated with increased LV mass and prevalence of anatomic LVH when repolarization is examined quantitatively on digital ECGs. Incorporation of ECG strain into scores that include standard voltage criteria improves ECG detection of LVH. ECG strain has also been associated with adverse prognosis in a variety of clinical populations, including patients with hypertension and implicated as the primary marker of untoward outcomes when ECG LVH criteria have been used for risk stratification. However, whether ECG strain is an independent predictor of cardiovascular (CV) morbidity and mortality after adjusting for the type and effectiveness of antihypertensive therapy is unclear.

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study demonstrated that therapy with losartan was more effective than atenolol in preventing CV morbidity and mortality in the setting of large and nearly identical reductions in systolic and diastolic pressure in both treatment arms. In the prespecified echocardiographic substudy of the LIFE study, strain on the baseline ECG was associated with greater LV mass and a higher prevalence of LVH, suggesting that ECG strain may also be associated with an increased risk of CV morbidity and mortality in LIFE. Therefore, the present study examined the relation of the strain pattern on the baseline ECG to major CV events in the LIFE study, independent of the effects of treatment type, baseline severity of hypertension and ECG LVH, and other potential risk factors.

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Methods

Subjects
The LIFE trial\textsuperscript{6,17} enrolled hypertensive patients with ECG LVH by Cornell voltage-duration product\textsuperscript{18} and/or Sokolow-Lyon voltage criteria\textsuperscript{1} on a screening ECG in a prospective, double-blind study large enough (n=1913) to demonstrate that an appreciable reduction in mortality and morbidity is associated with use of losartan as opposed to atenolol.16 Eligible patients for the LIFE study were men and women aged 55 to 80 with previously untreated or treated essential hypertension with mean seated blood pressure in the range 160 to 200/95 to 115 mm Hg after 1 and 2 weeks on placebo. A total of 8854 patients had baseline ECGs on which the strain pattern could be determined. There were 4770 women and 4084 men with mean age 67±7 years.

Electrocardiography

Hard-copy ECGs, recorded at either 25 or 50 mm/s paper speeds, were interpreted at the Core Laboratory at Sahlgrenska University Hospital/Ostra in Göteborg, Sweden, by experienced investigators blinded to clinical information. Using calipers, QRS duration was measured to the nearest 4 ms in all 12 leads, and R-wave amplitudes in leads aVL, V₅, and V₆ and S-wave amplitudes in leads V₁ and V₄ were measured to the nearest 0.5 mm (0.05 mV).\textsuperscript{17} The product of QRS duration times the Cornell voltage combination (R₉₋₁₄ + S₉₋₁₄ with 8 mm added in women\textsuperscript{18}) was used with a threshold value of 2440 mmms to identify LVH. As a consequence of new information published after the start of the LIFE trial\textsuperscript{6,17} and feedback from investigators, 2 changes were made in ECG entry criteria that affected patients enrolled after April 30, 1996: the gender adjustment of Cornell voltage was reduced from 8 to 6 mm and Sokolow-Lyon voltage (S₆₋₄ + RV₅₋₆ >38 mm) was accepted as an alternative ECG eligibility criterion.\textsuperscript{7}

Determination of the presence or absence of ECG strain as a dichotomous variable was visually assessed at Helsinki University Central Hospital as previously described.\textsuperscript{7} Repolarization abnormalities in leads V₁ and/or V₆ were considered consistent with the presence of typical strain when there was a downsloping convex ST segment with an inverted asymmetrical T-wave opposite to the QRS axis.\textsuperscript{14} In addition, T-wave amplitudes in leads V₅ and V₆, measured to the nearest 0.5 mm, were available in 6876 (77.7%) of the patients.\textsuperscript{20}

End Point Determination
The study used a composite end point of CV death, nonfatal myocardial infarction, or nonfatal stroke according to previously defined criteria.\textsuperscript{17} Potential end points were ascertained and then verified by an expert Endpoint Committee who were blinded to ECG results when classifying possible morbid events.\textsuperscript{34,35}

Statistics
Data management and analysis were performed with SPSS version 9 software. Data are presented as mean±SD for continuous variables and proportions for categorical variables. Differences in prevalences between groups were compared using \( \chi^2 \) analyses, and mean values of continuous variables were compared using an unpaired \( t \) test. To test the hypothesis that ECG strain at baseline was associated with an increased risk of CV events, the relation of strain to the risk of developing the LIFE composite clinical end point and its individual components was analyzed based on the intention-to-treat principle: All randomized patients were followed for end points for the duration of the study, regardless of protocol violations or adherence to study medication.16 All enrolled patients with a valid baseline ECG determination for strain were included in the statistical analyses.

Event rates were calculated and plotted according to the Kaplan-Meier product limit method. The relation of strain to the risk of clinical end points was assessed using Cox proportional hazards models, with a treatment group indicator included as a standard covariate. Treatment-adjusted hazard ratios for the incidence of the composite CV end point and its individual components were computed as the antilog of the estimated coefficient. The 95% confidence interval (CI) of each hazard ratio was calculated from the estimated coefficients and standard errors, and Wald \( \chi^2 \) statistics and probability values were calculated. To test the independence of ECG strain as a predictor of CV events, strain and treatment group were entered together into multivariate Cox models that also included as covariates age; gender; race; diabetes; history of ischemic heart disease; congestive heart failure; stroke; peripheral vascular disease or smoking; baseline urinal albumin/creatinine ratio; total and HDL cholesterol; body mass index; and baseline values of systolic and diastolic pressure, Cornell product, and Sokolow-Lyon voltage. For all tests, a 2-tailed \( P<0.05 \) was required for statistical significance.

Results

Patient Characteristics
ECG strain was present in 971 patients (11.0%) and the LIFE composite end point of CV death, nonfatal myocardial infarction, or stroke occurred in 1035 patients (11.7%). Clinical and demographic characteristics of patients according to the presence or absence of strain on the ECG are shown in Table 1. Compared with patients without ECG strain, patients with strain were older; were more likely to be male, black, and diabetic; were more likely to have a prior history of ischemic heart disease, congestive heart failure, stroke, and peripheral vascular disease; and had lower total and HDL cholesterol levels and higher urine albumin/creatinine ratios. Patients were similar with respect to mean body mass index and were evenly divided between the losartan and atenolol treatment arms.

The relationship of blood pressure and ECG LVH measurements at baseline and changes in these measurements between baseline and last in-study determination to the presence or absence of strain on the baseline ECG are shown in Table 2. Patients with strain had slightly higher baseline systolic pressures, but similar baseline diastolic pressures and similar changes in systolic pressure and diastolic pressure. ECG strain was associated with greater baseline severity of Cornell product and Sokolow-Lyon voltage LVH and with higher baseline prevalences of ECG LVH using both Cornell product (71.2% versus 65.1%, \( P<0.001 \)) and Sokolow-Lyon voltage criteria (44.1% versus 19.2%, \( P<0.001 \)). Despite similar reductions in systolic and diastolic pressure, patients with strain had significantly greater reductions in Sokolow-Lyon voltage during the course of the study. In contrast, there was no difference in the degree of regression of Cornell product LVH between patients with and without strain.

Electrocardiographic Strain and Prediction of Outcome
In Cox analyses that adjusted for the effect of treatment with losartan versus atenolol, presence of the strain pattern of lateral repolarization abnormality on the baseline LIFE study ECG was associated with an increased risk of CV morbidity and mortality and with an increased risk of all-cause mortality (Figures 1 and 2, Table 3). The 971 patients with strain on their baseline ECG had a 2-fold increased risk of the composite CV end point, with an actuarial 5-year event rate of 21.0% versus only 11.2% in those without ECG strain. Strain was associated with an increased risk of each of the component end points of the LIFE study. After adjusting for...
treatment effect, patients with strain had a 2.26-fold increased risk of CV mortality (5-year CV mortality 9.1% versus 4.3%), a 2.16-fold increased risk of myocardial infarction (5-year infarction rate 8.1% versus 3.9%), and a 1.76-fold increased risk of stroke (5-year stroke rate 10.2% versus 5.8%) compared with patients without strain. In addition, although all-cause mortality was not a prespecified LIFE end point, patients with ECG strain had a 1.85-fold increased risk of death from any cause (5-year mortality 14.6% versus 8.3%) compared with patients without strain.

Because patients with and without strain differed significantly with respect to demographic and clinical variables that could affect outcome (Tables 1 and 2), the independent relation of outcomes to the presence or absence of strain was examined after adjusting for the possible effects of treatment, age, gender, race, prevalent diabetes, history of ischemic heart disease, congestive heart failure, stroke or peripheral vascular disease, baseline urinary albumin/creatinine ratio, total and HDL cholesterol, and body mass index, and for the possible effects of baseline systolic and diastolic blood pressures, Cornell product, and Sokolow-Lyon voltage (Table 3). After adjusting for these factors, ECG strain remained a significant predictor of CV mortality, myocardial infarction, and the LIFE composite CV end point, but had only borderline statistical value for the prediction of stroke and all-cause mortality. Of note, neither quantitative measures of T-wave amplitude in leads V₅ and/or V₆ nor the dichotomous presence or absence of left atrial abnormality on the ECG added to the predictive value of the dichotomous strain variable in the subsets of the present population in which these measurements were available (n=6876 and n=8675, respectively).

**Discussion**

This study demonstrates that the presence of typical strain on the ECG in hypertensive patients with ECG LVH by Cornell product or Sokolow-Lyon voltage identifies patients at higher risk of CV morbidity and mortality in the setting of antihypertensive therapy associated with large decreases in systolic and diastolic pressure. The increased CV risk associated with ECG strain was independent of the improved prognosis with

<table>
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<th>Variables</th>
<th>Strain Absent (n=7833)</th>
<th>Strain Present (n=971)</th>
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<tr>
<td>Baseline measurements</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
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losartan therapy in the LIFE trial16 and persisted after adjusting for the greater baseline severity and prevalence of ECG LVH and the higher prevalence of other CV disorders in patients with strain. These results, taken together with findings in a subset of the LIFE echocardiographic substudy that resolution of the strain pattern between baseline and year-1 was associated with a 3-fold lower risk of echocardiographic hypertrophy compared with persistence of strain,21 suggest that serial quantitative assessment of ECG strain may prove useful in further stratifying risk and in identifying patients who may require additional antihypertensive therapy.

Electrocardiographic Strain and the Prediction of Outcome

Previous studies examining the relation of ECG strain to adverse outcomes have demonstrated varying prevalences and predictive value of this pattern in population-based studies.11–13,15,22 In 5581 participants in the Framingham Heart Study,11,12 the 190 (3.4%) with ECG LVH and ST depression and T-wave flattening or inversion had a 3-fold increased risk of developing coronary heart disease after adjusting for age, gender, and blood pressure. The Copenhagen City Heart Study22 of 11 634 participants with no evidence of ischemic heart disease at baseline found that Minnesota code definitions of ST depression and/or T-wave...
inversion remained predictive of cardiac events in multivariate analyses. However, these population-based studies used less specific definitions of strain than in the present study, had much lower prevalences of repolarization abnormalities than the LIFE study,\textsuperscript{11,12,22} and did not adjust for baseline severity of ECG LVH. In a serial analysis of 274 men and 250 women from the Framingham Study selected on the basis of having ECG LVH by Framingham Study criteria at 1 of 19 biennial exams,\textsuperscript{16} ECG strain by their criteria was present in 13% of men and 22% of women and was associated with age-adjusted risks of CV events of 5.84 (95% CI 3.55 to 9.62) and 2.47 (1.38 to 4.42), respectively. These risks remained relatively unaffected by further adjusting for baseline cholesterol, diabetes, and smoking status, and for baseline and serial changes in systolic pressure.\textsuperscript{13} Assessment of the presence or absence of the strain pattern over time provided further risk stratification, with new strain associated with increased risk and resolution of strain associated with decreased risk of CV events.\textsuperscript{13} In contrast, ECG strain was present in 11.1% of a population-based study of elderly men,\textsuperscript{15} but was not a significant univariate predictor of either all-cause or CV mortality.

The predictive value of ECG strain in patients with hypertension has been less extensively studied.\textsuperscript{9,10} In 439 hypertensive patients, Sokolow and Perloff\textsuperscript{9} found typical events.\textsuperscript{13} In contrast, ECG strain was present in 11.1% of a population-based study of elderly men,\textsuperscript{15} but was not a significant univariate predictor of either all-cause or CV mortality.

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Although the precise reasons why ECG strain leads to increased CV morbidity and mortality are not known, the strong association of strain with abnormalities of CV structure and function may in part explain the adverse prognosis associated with strain. In the present study strain was associated with greater baseline severity of ECG LVH, higher prevalences of male gender, black race, diabetes, history of various forms of heart and vascular disease, and evidence of greater renal end-organ damage as manifested by albuminuria. However, strain remained predictive of outcome in the current study after adjusting for the possible impact of these factors. In the echocardiographic substudy of LIFE,\textsuperscript{7} ECG strain was strongly related to the presence of coronary heart disease, increased LV mass, a higher prevalence of echocar-
diographic LVH that was more likely to be concentric, and lower myocardial contractility and higher estimated myocardial oxygen demand. Although the low number of events in this small subset of patients precludes meaningful analyses of the predictive value of strain after adjusting for echocardiographic LV mass, we have recently demonstrated that ST depression and echocardiographic LV mass measurements provide independent prognostic value in a separate population.23

Mechanisms of Abnormal Repolarization
In addition to the possible relation of lateral ST segment and T-wave changes to coronary disease, these ECG abnormalities may also reflect LVH and subendocardial ischemia in the absence of coronary disease.2 Development of the typical strain pattern in response to LVH is predicted by a distributed dipole model in which T-wave amplitudes are proportional to the square of the cell radius and flattening or inversion of the T wave is attributed to the contiguity effect of adjacent layers having different transmembrane action potential durations.24 The linear relations of increasing ST depression and T-wave inversion to increasing LV mass supports this hypothesis.8 In addition, ST depression and T-wave inversion may reflect true subendocardial ischemia in the absence of coronary disease, because of hypertrophy-induced compensatory increases in coronary artery size that are inadequate for the magnitude of increased LV mass and wall thickness.25-27 This hypothesis is supported by the association of strain with increased wall stress—heart rate product among hypertensive patients with ECG LVH but no evidence of coronary disease in the LIFE study,7 providing evidence of a demand-predisposition to myocardial ischemia in these patients. The finding that the ratio of coronary lumen area to regional LV mass can at least partially normalize in the setting of regression of LVH following aortic valve replacement for aortic stenosis28 suggests that the repolarization abnormalities of strain may also diminish or disappear in the setting of regression of hypertrophy associated with antihypertensive therapy. The association of resolution of the strain pattern between baseline and year-1 of the LIFE study with a therapy. The association of resolution of the strain pattern over time in the entire LIFE study population and by the lack of information on the serial behavior of the strain pattern over time in the entire LIFE study population and by the absence of quantitative data assessing the degree of ST depression in this population. Although serial assessment of the presence or absence of strain provide additional prognostic information in a subset of the Framingham population,13 whether evaluation of the time-course of strain on the ECG provides additional risk information in hypertensive patients undergoing treatment will require further evaluation. Although quantitative measures of T-wave amplitude did not add to the prognostic value of ECG strain in a large subset of the current population, previous observations that analysis of the degree of ECG strain as measured by ST depression in the lateral leads is strongly related to the presence and severity of LVH8 taken together with the complimentary prognostic value of measured ST depression and echocardiographic LVH23 suggest that serial assessment of the magnitude of lateral repolarization abnormality may provide additional prognostic information in hypertensive patients.

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References


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