Importance of the Electrocardiographic Strain Pattern in Patients With Resistant Hypertension

Gil Salles, Claudia Cardoso, Armando R. Nogueira, Katia Bloch, Elizabeth Muxfeldt

Abstract—The electrocardiographic strain pattern is a marker of left ventricular hypertrophy and adverse cardiovascular prognosis. The objective of this study was to assess the factors associated with the presence of ECG strain in patients with resistant hypertension and, specifically, to evaluate the relationships between strain and left ventricular mass (LVM) and structure. In a cross-sectional design, 440 resistant hypertensive subjects were evaluated. Clinical, laboratory, electrocardiographic, 24-hour ambulatory blood pressures, and echocardiographic variables were obtained. Statistical analysis involved bivariate tests, analysis of covariance, and multivariate logistic regression. An ECG strain pattern was present in 101 patients (23%). Patients with strain were more frequently men with lower body mass index, had more target-organ damage, higher 24-hour blood pressure, higher serum creatinine and 24-hour microalbuminuria, and more prolonged QT interval duration than those without strain. After controlling for all covariates, the presence of strain remained associated with increased LVM and wall thicknesses, both in all patients and also in those with echocardiographic left ventricular hypertrophy. Furthermore, the presence of ECG strain was associated with increased LVM ($P<0.001$), higher 24-hour systolic blood pressure ($P<0.001$), prolonged maximum QTc-interval duration ($P<0.001$), lower waist circumference ($P=0.009$), male gender ($P=0.011$), physical inactivity ($P=0.020$), higher serum creatinine ($P=0.031$) and fasting glycemia ($P=0.027$), and the presence of coronary heart disease ($P=0.001$) and peripheral arterial disease ($P=0.045$). Thus, in resistant hypertension patients, the presence of ECG strain is independently associated with increased left ventricular wall thicknesses and mass and also with other potentially adverse factors. These relationships offer insight into the known association between strain and unfavorable cardiovascular prognosis.

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Key Words: echocardiography ■ electrocardiography ■ hypertension, arterial ■ hypertrophy

The classic left ventricular (LV) strain pattern of ST-segment depression and T-wave inversion on the left precordial leads of the standard resting ECG is a well-known marker of the presence of anatomic LV hypertrophy (LVH).1–6 Moreover, the occurrence of this electrocardiographic abnormality of ventricular repolarization has been associated with a worse prognosis both in hypertensive subjects3,6 and in general populations.7,8 Indeed, when several electrocardiographic LVH criteria have been considered for cardiovascular risk stratification, the strain pattern was implicated as the strongest marker of adverse outcomes.7–9,11 Moreover, the strain pattern has been associated not only with underlying coronary heart disease3,6 but also with cardiovascular risk factors, such as higher blood pressure levels, diabetes, older age, and male gender.6–10,12 Thus, these relationships could, at least in part, explain the untoward clinical consequences of this ECG finding beyond those directly attributable to high LV mass (LVM) and hypertrophy.3,6,11

However, the independent associations of ECG strain with LVM and other factors have not been extensively investigated.6,13 It has not been established yet whether in patients with echocardiographically demonstrated LVH the presence of ECG strain is associated with higher LVM. This knowledge is potentially important, because the presence of ECG strain may provide additional prognostic information beyond that obtained from echocardiographic LVH.

So, the aim of this study was to investigate in a large group of resistant hypertensive patients the importance of the relationships between the presence of the ECG strain pattern and other clinical, laboratory, 24-hour ambulatory blood pressure (BP) monitoring (ABPM) and electrocardiographic variables, and, specifically, to assess whether patients with ECG strain have increased LVM after controlling for other variables that could potentially impact this association.

Methods

Subjects and Baseline Procedures

This was a cross-sectional study involving 471 patients with resistant hypertension (RH) 27.6% men; mean age: 59.9 years; SD: 11.7 years) enrolled between January 2000 and September 2004. All of the participants gave written informed consent, and the local ethics committee had approved the study protocol previously. The charac-
teristics of this cohort, as well as the baseline procedures and the diagnostic definitions, have already been detailed elsewhere.14,15 In brief, all of the hypertensive subjects referred who fulfilled criteria for RH (office BP ≥140/90 mm Hg using ≥3 antihypertensive drugs in full dosages always including a diuretic) were submitted to a standard protocol that included a thorough clinical examination, laboratory evaluation, 12-lead ECG, 24-hour ABPM, and 2D echocardiography. Compliance to antihypertensive treatment was evaluated in the first interview by a validated standard questionnaire.16 Only patients considered medium or highly adherent to treatment were enrolled into the study. In clinical interview, demographic and anthropometric characteristics (sex, age, race, weight, height, and waist circumference), cardiovascular risk factors (diabetes, dyslipidemia, smoking, physical inactivity, and obesity), and target-organ damage (coronary heart disease [CHD], heart failure, cerebrovascular disease, advanced retinopathy, and peripheral arterial disease) were recorded. In particular, CHD was diagnosed by history of angina at rest or previous myocardial infarction or revascularization procedures, or by the presence of ECG pathological Q-waves (Minnesota codes: 1.1 and 1.2) or echocardiographic segmental wall motion abnormalities. BP was measured twice by a trained physician, with patients in the sitting position, using a calibrated mercury sphygmomanometer and a suitably sized cuff. First and fifth Korotkoff’s sounds were the criteria for systolic (SBP) and diastolic BP (DBP), and BP considered was the mean between the 2 readings.17 Pulse pressure (PP) was calculated as SBP minus DBP. Laboratory evaluation included fasting glycemia, serum creatinine, and lipid proﬁles. Microalbuminuria, proteinuria, and creatinine were measured as the ratio of 24-hour protein excretion to body surface area (LVMI) and, alternatively, to height2.7. Echocardiographic LVH was defined as LVMI >140 g/m2 in men and >116 g/m2 in women. Relative wall thickness (RWT) was calculated as the ratio of 2PWT/LVEDD) and considered in- creased if ≥0.43. Patterns of LV geometry were deﬁned according to LVM and RWT: (1) normal (no LVH, normal RWT); (2) concentric remodeling (no LVH, increased RWT); (3) eccentric hypertrophy (LVH, normal RWT); and (4) concentric hypertrophy (LVH, increased RWT).

Statistical Analysis

Continuous data were described as means and SDs. Bivariate com- parisons between patients with and without ECG strain pattern were performed by unpaired t test in normally distributed data and by nonparametric Mann–Whitney test in asymmetrically distributed data. Categorical data were compared by χ2 test. Associations with ECG strain were determined by stepwise multivariate logistic regres- sion analysis. All of the variables with a P<0.20 in bivariate analysis entered into the multivariate analysis in a backward selection procedure. Odds ratios with their 95% CIs were calculated for each independently associated variable. For continuous variables, Odds ratios were calculated for increments of 1 SD. Finally, echocardiographic variables were further compared using ANCOVA to adjust for all of the baseline differences in clinical-demographic, labora- tory, 24-hour ABPM, and electrocardiographic variables between patients with and without ECG strain. A similar analysis was also performed exclusively for the subgroup of patients with established echocardiographic LVH. All of the statistics were performed by SPSS statistical package version 13.0, and a 2-tailed P<0.05 was regarded as significant.

Results

Baseline Characteristics of Patients With and Without ECG Strain

Typical LV strain pattern was presented on ECGs of 101 patients (23%). Tables 1 and 2 show clinical–demographic office and ambulatory BPs and laboratory and electrocardiographic variables in patients with and without ECG strain. Patients with strain were more frequently men, had lower body mass index and waist circumference, and had a lower prevalence of dyslipidemia than those without strain, although serum levels of total and high-density lipoprotein cholesterol and triglycerides were similar between the 2 groups. Patients with ECG strain had a higher prevalence of physical inactivity, more target-organ damage, and used more antihypertensive drugs than subjects without strain. All of the BPs, except office DBP, were signiﬁcantly higher in patients with ECG strain. Also, patients with strain had decreased nocturnal BP reductions and a higher prevalence of the non-dipper pattern of circadian BP variation. Patients with ECG strain had higher serum creatinine and 24-hour urinary albumin excretion than subjects without strain. Finally, pa- tients with strain had signiﬁcantly prolonged maximum QTc interval duration and higher QRS voltages in comparison with those without the ECG strain pattern.

Multivariate Associates With ECG Strain

Table 3 presents the results of multivariate logistic regression analysis for variables independently associated with the presence of the strain pattern on ECG. Increased LVMi was the strongest independently associated variable with strain. Other variables selected were increased 24-hour SBP, prolonged maximum QTc interval duration, lower waist circumference, male gender, physical inactivity, greater number of drugs in antihypertensive treatment, the presence of CHD and peripheral arterial disease at baseline, and increased fasting glycemia and serum creatinine.
Patients With Strain (n=101) | Patients Without Strain (n=339) | P
---|---|---
Demographic characteristics | | |
Male gender | 42.6% | 24.4% | 0.001
Age, y | 60.8 (11.9) | 59.9 (11.8) | 0.50
Body mass index, kg/m² | 29.1 (5.3) | 30.4 (5.7) | 0.048
Cardiovascular risk factors | | |
Diabetes | 36.0% | 33.2% | 0.63
Dyslipidemia | 53.5% | 65.0% | 0.044
Physical inactivity | 82.2% | 68.7% | 0.008
Waist circumference, mm | 984 (104) | 1000 (118) | 0.24
Target organ damage | | |
CHD | 45.0% | 28.0% | 0.002
Heart failure | 12.2% | 3.4% | 0.002
Cerebrovascular disease | 24.0% | 13.1% | 0.012
Peripheral arterial disease | 15.3% | 5.0% | 0.001
Office BP measurements | | |
No. of antihypertensive drugs | 3.8 (0.8) | 3.5 (0.6) | 0.007
Office SBP, mm Hg | 194.9 (34.0) | 180.4 (28.4) | <0.001
Office DBP, mm Hg | 102.7 (24.3) | 101.3 (18.7) | 0.60
Office PP, mm Hg | 92.2 (30.4) | 79.1 (22.6) | <0.001
Laboratory exams | | |
Fasting glycemia, mmol/L | 6.9 (2.7) | 6.4 (2.4) | 0.08
S-creatinine, μmol/L | 107 (49) | 89 (36) | <0.001
S-total cholesterol, mmol/L | 5.65 (1.24) | 5.77 (1.28) | 0.42
S-HDL cholesterol, mmol/L | 1.23 (0.34) | 1.25 (0.33) | 0.50
S-triglycerides, mmol/L | 1.69 (0.84) | 1.77 (1.02) | 0.39
Microalbuminuria >30 mg/24 h | 45.5% | 31.8% | 0.013

Values are means (SD) or proportions in percentages. S indicates serum; HDL, high density lipoprotein.

Echocardiographic Findings in Relation to ECG Strain

Relationships between LV structure and the presence or absence of ECG strain pattern are presented in Table 4. Patients with strain had significantly greater LV wall thicknesses, diastolic LV internal dimension, and LVM either indexed to body surface area or to height than patients without strain, even after adjustment to other potential confounders, especially the presence of clinical CHD. The same was observed in the subgroup of patients with established echocardiographic LVH. Second, it demonstrates that beyond increased LVM, the presence of ECG strain is also independently associated with other adverse factors: increased 24-hour SBP, prolonged maximum QTC-interval duration, higher serum creatinine and fasting glycemia, physical inactivity, and with the presence of 2 important target-organ damage types (CHD and peripheral arterial disease). The only potentially favorable factor associated with strain was a lower waist circumference.

These findings offer insights into the known association between the ECG strain pattern and untoward cardiovascular prognosis in hypertensive patients2–8 and in general populations,9–10,20 suggesting that the presence of ECG strain may provide additional prognostic information beyond that derived from echocardiographic LVH and mass. Only 1 previous study20 addressed this hypothesis, showing that the degree of ST segment depression measured at the microvolt level, a possible quantitative measurement of ECG strain, added prognostic information to echocardiographic LVH for mortality, although only a few individuals actually had enough ST depression to fulfill criterion for typical ECG strain.20 Clearly, this important question shall be further addressed in future well-designed prospective studies.

Although many previous investigations1–5 have demonstrated associations between the presence of classical strain pattern on ECG and LVH, only 2 studies specifically evaluated the relationships between ECG strain and echocardiographic LV structure and mass,6,13 one of them13 using the quantitative measurement of ST depression as a reflection of strain. Both studies support our findings that patients with strain had significantly higher LV wall thicknesses and mass than patients without strain, even after controlling for baseline differences between them. Moreover, the present study demonstrates that in patients with already established echocardiographic LVH, the presence of typical ECG strain pattern is also independently associated with increased LV wall thicknesses and mass. As far as we know, this finding is new and potentially important for cardiovascular risk stratification. Also, patients with strain showed a greater prevalence of the concentric hypertrophy LV geometric pattern in accordance with that reported in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study.6

The other independent factors associated with the presence of ECG strain pattern, higher 24-hour SBP, male gender, increased serum creatinine and fasting glycemia (or a greater prevalence of diabetes), and greater prevalences of CHD and peripheral arterial disease, have all been demonstrated in previous studies to be associated with ECG strain.3,6–9,12,13

Regarding 24-hour ABPM parameters, only one previous investigation7 evaluated their relationships with the presence of ECG strain. Our findings support this study, showing that
patients with strain have higher ambulatory BPs (systolic, diastolic, or PP), either during daytime or nighttime, than those without ECG strain. The implications for cardiovascular prognosis are clear, because ABPM is superior to office BPs for cardiovascular risk stratification.21 Furthermore, patients with strain have a decreased nocturnal BP fall and a higher prevalence of the nondipper status, another potential adverse prognostic marker derived from ABPM.22

The association between the presence of ECG strain and QTc interval prolongation has not been explored before but is not unexpected. QTc interval prolongation has been associated with LVH14 and is a well-known marker of abnormal ventricular repolarization.23 The typical ECG strain pattern is also an abnormality of ventricular repolarization secondary to anatomic myocardial cell hypertrophy24 and to subendocardial ischemia with or without underlying CHD.3,25 Individuals with QT interval prolongation are at increased risk for the occurrence of life-threatening ventricular arrhythmias.23 Thus, this relationship may help to explain the adverse cardiovascular outcomes of patients with strain, particularly in relation to sudden arrhythmic death.

An unexpected finding of this study was the relation between body mass and ECG strain. Patients with strain were leaner than those without strain in bivariate analysis, and a lower waist circumference remained as one of the independent factors associated with ECG strain in multivariate analysis. This association may reflect a real demographic difference between subjects with and without ECG strain in a similar manner to that reported in the LIFE study26 in relation to obesity and Sokolow–Lyon voltage criterion for LVH.

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Some limitations of the present study are important to note. Its cross-sectional design prevents firm conclusions about the associations found, and no inferences about ECG strain development or regression over time can be made. Another potential flaw of this study is the fact that no provocative test to diagnose silent CHD, a factor that potentially affects the occurrence of ECG strain, was performed. So, the statistical adjustment for the presence of CHD may have been in-

### Table 2. 24-Hour Ambulatory Blood Pressure and Electrocardiographic Variables in RH Patients With and Without Electrocardiographic LV Strain Pattern

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients With Strain (n=101)</th>
<th>Patients Without Strain (n=339)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ABPM measurements</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-h mean SBP, mm Hg</td>
<td>147.1 (20.9)</td>
<td>136.4 (18.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-h mean DBP, mm Hg</td>
<td>83.8 (13.1)</td>
<td>79.0 (12.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>24-h mean PP, mm Hg</td>
<td>63.3 (15.3)</td>
<td>57.5 (13.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Daytime mean SBP, mm Hg</td>
<td>149.1 (21.6)</td>
<td>138.9 (18.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Daytime mean DBP, mm Hg</td>
<td>85.4 (14.0)</td>
<td>81.2 (12.8)</td>
<td>0.005</td>
</tr>
<tr>
<td>Daytime mean PP, mm Hg</td>
<td>63.6 (15.1)</td>
<td>57.6 (13.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nighttime mean SBP, mm Hg</td>
<td>140.1 (22.9)</td>
<td>127.3 (22.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nighttime mean DBP, mm Hg</td>
<td>77.1 (13.8)</td>
<td>71.4 (14.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nighttime mean PP, mm Hg</td>
<td>63.0 (16.0)</td>
<td>55.9 (15.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nighttime SBP reduction, %</td>
<td>5.9 (8.5)</td>
<td>8.5 (8.4)</td>
<td>0.007</td>
</tr>
<tr>
<td>Nighttime DBP reduction, %</td>
<td>9.4 (9.8)</td>
<td>12.1 (9.9)</td>
<td>0.016</td>
</tr>
<tr>
<td>Nondipper status</td>
<td>74.3%</td>
<td>60.1%</td>
<td>0.010</td>
</tr>
<tr>
<td><strong>Electrocardiographic measurements</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum QTc duration, ms(^{1/2})</td>
<td>465.6 (42.7)</td>
<td>442.5 (32.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sokolow–Lyon voltage, mV</td>
<td>3.68 (0.99)</td>
<td>2.48 (0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted* Cornell voltage, mV</td>
<td>2.74 (0.96)</td>
<td>1.98 (0.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cornell voltage product, mV.ms</td>
<td>262.0 (91.6)</td>
<td>185.5 (91.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are means (SD) or proportions in percentages.
*Cornell voltage with 0.6 mV added in women.

### Table 3. Results of Multivariate Logistic Regression Analysis for Variables Independently Associated With the Presence of Electrocardiographic Strain Pattern in Patients With RH

<table>
<thead>
<tr>
<th>Variable</th>
<th>SD*</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass index, g/m²†</td>
<td>43</td>
<td>1.66</td>
<td>1.25–2.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-hour mean SBP, mm Hg</td>
<td>20</td>
<td>1.62</td>
<td>1.22–2.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum QTc duration, ms(^{1/2})</td>
<td>35</td>
<td>1.57</td>
<td>1.21–2.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHD, pres. vs abs.</td>
<td>2.50</td>
<td>1.42–4.38</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Waist circumference, mm</td>
<td>116</td>
<td>0.66</td>
<td>0.49–0.90</td>
<td>0.009</td>
</tr>
<tr>
<td>Male gender</td>
<td>2.20</td>
<td>1.19–4.06</td>
<td>0.011</td>
<td></td>
</tr>
<tr>
<td>No. of antihypertensive drugs</td>
<td>1</td>
<td>1.62</td>
<td>1.11–2.37</td>
<td>0.013</td>
</tr>
<tr>
<td>Physical inactivity, pres. vs abs.</td>
<td>2.24</td>
<td>1.13–4.44</td>
<td>0.020</td>
<td></td>
</tr>
<tr>
<td>Fasting glycemia, mmol/L</td>
<td>2.6</td>
<td>1.36</td>
<td>1.03–1.78</td>
<td>0.028</td>
</tr>
<tr>
<td>S-creatinine, μmol/L</td>
<td>40</td>
<td>1.30</td>
<td>1.02–1.64</td>
<td>0.031</td>
</tr>
<tr>
<td>Peripheral arterial disease, pres. vs abs.</td>
<td>2.53</td>
<td>1.02–6.28</td>
<td>0.045</td>
<td></td>
</tr>
</tbody>
</table>

pres. vs abs. indicates present vs absent.
*For continuous variables, odds ratios were calculated for increments of 1 SD.
†Indexed to body surface area.
complete, and we cannot with certainty rule out the possibility that subclinical CHD might be residually affecting our findings.

Perspectives
This study with a large group of patients with RH provides evidence that the presence of the classic ECG strain pattern is independently associated with higher LV wall thicknesses and mass and also with other unfavorable cardiovascular risk factors, such as increased 24-hour BP, prolonged QTc interval duration, increased serum creatinine and glycemia, male gender, and atherosclerotic vascular disease. It needs to be further studied prospectively whether the presence of ECG strain confers additional cardiovascular risk stratification over and above that derived from echocardiographic LVH and mass. Moreover, it remains to be established whether multifactorial interventions are capable of regressing the ECG strain pattern and decreasing the high cardiovascular risk profile of resistant hypertensive patients with strain.

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Disclosures
None.

References


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