Title

Diagnostic sensitivity of electrocardiograms in left ventricular hypertrophy according to gender and increase in cardiac mass

Short title: ECG: degrees of LVH and gender

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Abstract

**Background and objectives:** Left ventricular hypertrophy (LVH), diagnosed by electrocardiography (ECG) or echocardiography, is an independent predictor of cardiovascular risk. The objective of the present study was to analyze the influence of gender on the sensitivity of some of the criteria used for the detection of LVH, according with the progression of the degree of ventricular hypertrophy.

**Methods:** ECGs of 874 hypertensive patients with LVH on echocardiography were analyzed and divided by gender in mild, moderate and severe LVH. Sensitivity of ECG to detect LVH in men and women according to the increase in ventricular mass was studied.

**Results:** 874 patients were analyzed (265 men, 30.3%; 609 women, 69.7%). The [(S + R) X QRS], Sokolow-Lyon, Romhilt-Estes, Perugia and strain pattern criteria showed high discriminatory power in the diagnosis of LVH in men and women in the three LVH groups, with better performance in men, especially for the [(S + R) X QRS] and Perugia scores.

**Conclusion:** The diagnostic sensitivity of ECG increases with progression of LVH and is higher in men, especially for [(S + R) X QRS] and Perugia scores.

**Keywords:** Electrocardiogram, Gender, Hypertension, Left ventricular hypertrophy
LVH is an independent predictor of morbidity and mortality in the general population when diagnosed both by ECG and echocardiography\textsuperscript{1,2}.

Since the pioneering observations from the Framingham Heart Study, several epidemiological studies have pointed out LVH as one of the most important risk factors for angina pectoris, myocardial infarction, heart failure, stroke and sudden death\textsuperscript{3}.

Among the different methods for the diagnosis of LVH, ECG is the less costly, the most widely available and easy-to-interpret method; it has high specificity, but low diagnostic sensitivity. However, despite this limitation, it remains an ancillary test widely used in the clinical practice as well as in several population-based studies, both on the prevention and on the analysis of the regression of the hypertrophic process\textsuperscript{3,4}. Also, ECG is highly reproducible and is very useful in the clinical follow-up of the patients.

Some factors may impact on the sensitivity of ECG in the diagnosis of LVH, gender being one of the most important\textsuperscript{5-7}.

The objective of the present study was to analyze the influence of gender on the sensitivity of some of the criteria used for the detection of LVH, according with the progression of the degree of ventricular hypertrophy.
**Material and methods**

**Patients**

In the period from March 2006 to December 2009, the 12-lead electrocardiograms of 874 hypertensive patients followed up on an outpatient basis and using antihypertensive medication regularly were analyzed. Patients with valvular heart disease; acute or chronic coronary artery disease; previous myocardial infarction; Chagas disease; rhythm disturbances; bundle branch block; use of digitalis; pre-excitation syndromes; large left ventricular (LV) mass; poor technical quality of echocardiography; or any other condition that could potentially cause distortion of the LV geometry and of the electrocardiographic analysis were excluded. The Research Ethics Committee of *Universidade Federal de São Paulo – Escola Paulista de Medicina* (UNIFESP-EPM) approved the study protocol, which is in agreement with the principles of the Declaration of Helsinki.

**Electrocardiogram**

Resting 12-lead ECG was performed with the patient in the supine position, sweep speed of 25 mm/s, and calibration set at 1.0 mV/cm (Dixtal EP3 device, Brazil). The tracing was decoded and, for the analysis of the different variables, a magnifier was used which permitted a five-fold magnification of the side in contact with the tracing, for a more accurate analysis. A single observer – a highly experienced cardiologist, quantified the following parameters: QRS complex duration and axis; R-wave amplitude in leads D1, aVL, V5 and V6; S-wave amplitude in V1, V2 and V3; the strain pattern in V5 and V6; and the largest amplitude of R and S-waves in the horizontal
plane leads. Eight electrocardiographic criteria for LVH were analyzed separately:

1. Largest S + largest R in the horizontal plane multiplied by the longest QRS duration \([S + R] \times QRS\]: sum of the largest amplitude of the S-wave and the largest amplitude of the R-wave in the horizontal plane (in mm), multiplied by the longest QRS complex duration (in seconds), usually in leads V₂ or V₃. LVH is defined by ECG when this score is \(\geq 2.8 \text{mm.s}^8\).

2. Sokolow-Lyon voltage criterion: \(SV_1 + RV_5 \text{ or } V_6 \geq 35 \text{mm}^9\).

3. Cornell voltage criterion: \(RaV_L + SV_3 \geq 20 \text{ mm for women, and} \geq 28 \text{ mm for men}^{10}\).

4. Cornell duration criterion: \((RaV_L + SV_3) \times QRS \text{ duration} \geq 2440 \text{ mm.ms}^{11}\); for women, add 8 mm

5. Romhilt-Estes point-score: largest amplitude of R or S \(\geq 30\) mm in the horizontal plane or \(\geq 20\) mm in the frontal plane, or stain pattern in V₅ or V₆ (worth only one point if patient is taking digitalis) or left atrial enlargement as determined by Morris index (three points); \(\hat{A}QRS\) electrical axis above minus 30 degrees (two points); and QRS duration \(\geq 90 \text{ ms in } V_5 \text{ or } V_6\) or ventricular activation time \(\geq 50 \text{ ms in } V_5 \text{ or } V_6\) (one point). Using this score, LVH is diagnosed when the sum is \(\geq 5\) points\(^{12}\).

6. R wave in aV\(_L\) \(\geq 11 \text{ mm}^{13}\).

7. Perugia score: LVH is diagnosed by the presence of one or more of the following findings: Cornell criterion, considering the limit of \(\geq 20 \text{ mm for women and } \geq 24 \text{ mm for men, Romhilt-Estes score and strain pattern}^{14}\).
8. Presence of the strain pattern: defined as a convex ST-segment depression with asymmetrical T-wave inversion opposed to the QRS complex in leads V5 or V6.

The analysis of reproducibility of the method was carried out by three observers who independently interpreted 100 ECG tracings randomly retrieved for analysis of R and S-wave amplitudes and QRS-complex duration.

Transthoracic echocardiography

The imaging studies were performed in the Department of Doppler Echocardiography, UNIFESP-EPM (ATL 1500 device, USA), with 2.0 and 3.5 MHz transducers. The patient was positioned in the left lateral position and the images were obtained from the left parasternal region between the fourth or fifth intercostal spaces; the usual views were used for a complete study on M and two-dimensional modes, with simultaneous ECG recording. According to the recommendations of the Penn Convention, the following measurements were taken: systolic and diastolic LV size; ventricular septal thickness; end-diastolic LV posterior wall thickness; end-diastolic and end-systolic volumes; diastolic shortening fraction; and ejection fraction using the cube method. LV mass was calculated using the formula: 

\[ \text{LV mass} = 0.8 \times \{1.04 \times [(\text{DIVS} + \text{LVEDD} + \text{PPVED})^3 - (\text{DDVE})^3]\} + 0.6 \text{ g}^{15}, \]

where DIVS is the diastolic interventricular septal thickness, LVEDD is the left ventricular end-diastolic diameter, and DLVPW is the diastolic LV posterior wall. LV mass was indexed for body surface for the adjustment of different heart sizes to variations in patient size. Body surface was calculated
using the formula: $BS = (W - 60) \times 0.01 + H$, where $BS$ is the body surface in m$^2$; $W$ is the weight in Kg; and $H$ is the height in meters$^{16}$. Body mass index (BMI) was calculated by dividing weight (Kg) by the square height (m). The patients were divided by gender and degree of ventricular hypertrophy, as calculated by echocardiography, according to recommendations of the American Society of Echocardiography/European Association of Echocardiography$^{17}$, as summarized in Table 1. Thus, for the female population, mild LVH was defined when the left ventricular mass index (LVMI) was between 89-100 g/m$^2$; moderate LVH when LVMI was between 101-112 g/m$^2$; and severe LVH when LVMI was above 113 g/m$^2$. For the male population, in turn, mild LVH was defined when LVMI was between 103-116 g/m$^2$; moderate LVH when LVMI was between 117-130 g/m$^2$; and severe LVH when LVMI was above 131 g/m$^2$. The diagnostic sensitivity of the eight electrocardiographic methods assessed in this study, with the three degrees of hypertrophy described, was analyzed and the results obtained were compared between men and women.

**Statistical analysis**

Continuous variables were expressed as mean and standard deviation. Categorical variables were expressed as percentage. All the significance probabilities (p values) shown are two-tailed. The Kappa test$^{18}$ was used for the analysis of reproducibility. In this test, values above 0.75 are considered excellent; those below 0.40 show poor agreement; and those between 0.40 and 0.75 show good agreement.
In order to verify the statistical significance, 95% confidence intervals and p < 0.05 were used in all comparisons.

**Results**

Of the 874 patients included in the study, all with echocardiographic LVH, 265 were males (30.3%) and 609 were females (69.7%), with a mean age of 59.7 ± 10.8 years. Table 1 shows the distribution by gender and by degree of LVH, as well as the overall characteristics of the study sample.

As regards the sensitivity values, we observed that almost all the electrocardiographic criteria are more efficient in diagnosing LVH in the male population, except for the Cornell-voltage criterion, which was the only one with better performance among women in the three degrees of LVH, although statistically significant only in the severe LVH group. Only the [(S + R) X QRS] and Cornell-voltage criteria showed progressive percentage of sensitivity according to the increase in the degree of LVH. In the study population, the [(S + R) X QRS], Sokolow-Lyon, Romhilt-Estes, Perugia and strain pattern criteria showed high discriminatory power in the diagnosis of LVH among men and women in the three degrees of hypertrophy, with a much better performance among the male population, especially for [(S + R) X QRS] and Perugia score, as demonstrated in Table 2.

As regards the analysis of reproducibility, the level of agreement between the three observers ranged from 0.82 to 0.98, which is considered excellent. The first figure corresponds to the QRS-complex duration and the second to the amplitude of R and S waves.
Discussion

LVH is a marker of high cardiovascular risk regardless of comorbidities, with no differences between ethnic groups, presence or absence of systemic hypertension or coronary artery disease, both in clinical and in epidemiological studies, and a close relationship between LVH and adverse cardiovascular events is clear. This is why it is important to detect LVH by low-cost diagnostic methods easy to apply in large populations; equally important is the knowledge of the interference of specific populations, as is the case of the male and female genders, obese individuals, the elderly, and smokers\textsuperscript{6,19,20,21}.

LVH usually leads to an increased amplitude of the QRS complex, with subsequent posterior and leftward deviation of the electrical forces, which originate deep S waves in right precordial leads. On the other hand, the greater cross-sectional ventricular activation resulting from LVH leads to increased QRS duration and incremental deflection (interval between the beginning of inscription and the maximum point of the QRS complex in left precordial leads)\textsuperscript{3,5}.

In the present study, transthoracic echocardiography was used as a reference for the diagnosis of LVH. The modified Devereux formula\textsuperscript{15} shows good correlation with left ventricular mass in necropsy studies ($r = 0.90; p < 0.001$), and is applicable to ventricles with normal geometric shape considered ellipsoid and within standards that permit the extrapolation of volume using the cube formula. This imaging study unquestionably represents a great advance in the diagnosis of several diseases, LVH included. However,
its cost is much higher than that of ECG, and it is also subject to methodological limitations regarding reproducibility, since it depends a great deal on the observer, and this limits its use in epidemiological studies. As previously underscored, the electrocardiographic diagnosis of LVH is known to be influenced by some factors such as age, obesity, smoking status and gender, the latter being the object of the present study. Levy et al. demonstrated in patients of the Framingham Health Study that the prevalence of LVH in echocardiographic studies was higher among women than among men, but this finding was not electrocardiographically confirmed (women = 5.6%; men = 9.0%; p = 0.075).

In our study sample, the patients were divided by gender and by progressive degrees of LVH. ECG is known to be a test with high specificity and low sensitivity in the detection of LVH in the overall population of individuals with hypertrophic hearts. However, the behavior of the accuracy of this method in progressive degrees of left ventricular mass is unknown, as hypertrophy of the myocardial cell increases the muscle mass globally, but this does not necessarily mean more generation of electrical potential. In fact, the contradiction between a hypertrophied left ventricle and the absence of increased QRS-complex may be explained by the larger amount of collagen fibers in the heart. The development of these fibers is concomitant to the process of LVH. As a result, the cardiac fibers become isolated, and this leads to ischemia, cell death and reparation with replacement for more collagen tissue. Thus, although the heart
mass is increased, its ability to generate electrical potential may even be decreased\textsuperscript{22,23}. It is important to notice that the age, body surface, and body mass index variables were very similar in both genders, and this practically excludes the interference of these factors on LVMI results.

Okin et al\textsuperscript{24} studied 389 patients of whom 116 had LVH and suggested that the poorer performance of ECG in women may be partially attributed to the lower voltage and QRS-complex duration due to the differences in body surface and heart sizes observed between the genders. On the other hand, indexation of the left ventricular mass is known to practically eliminate this problem\textsuperscript{15}.

The analysis of the diagnostic sensitivity of ECG, which was the major purpose of the present study, showed excellent performance of the \[(S + R) \times \text{QRS}\], Sokolow-Lyon voltage, Romhilt-Estes, Perugia and strain pattern criteria, especially with the progression of the degree of hypertrophy, thus confirming that ECG is more efficient in diagnosing LVH in the male population, maybe as a reflex of the greater expression of the QRS complex (amplitude and duration) among men\textsuperscript{24}. Contrary to this reasoning, the exception was the Cornell-voltage criterion which, in the three degrees of LVH, showed better performance among women, although with statistical significance only in the group with severe LVH.

Alfakih et al study\textsuperscript{7} evaluated three of the methods used in our study, and their gold-standard for comparison of LVH was magnetic resonance imaging. The authors demonstrated that the Cornell-voltage and Cornell duration criteria were more efficient in the
diagnosis of LVH in men, whereas the Sokolow-Lyon product criterion was superior in the female population. Costa et al\textsuperscript{25} studied patients with stage-5 chronic renal disease, among whom the prevalence of LVH was 83\% and the mean LVMI was $154.9 \pm 57.3$ g/m$^2$, and also showed that the Sokolow-Lyon voltage, Sokolow-Lyon product, Cornell voltage, Cornell product and Romhilt-Estes criteria diagnosed LVH more frequently in the male population.

In the present study, the analysis of the $[(S + R) \times QRS]$ score, which, in the original study with 1204 patients with controlled hypertension found sensitivity of 35.2\% and specificity of 88.7\% for the diagnosis of LVH, there was also good sensitivity, especially in the male population. This criterion, which uses the sum of the higher R-wave and the higher S-wave in the horizontal plane multiplied by the longest QRS-complex duration, is consistently supported by the physical point of view, because the relationship between increased electrical activity in LVH is expressed by a spatial vector which possesses amplitude and duration. The greater expression of R and S-waves, as well as of the QRS-complex, represented by this vector, showed good correlation with the left ventricular mass$^8$.

In conclusion, based on the present case series, the performance of ECG in the diagnosis of LVH, as expected, improves as the left ventricular mass increases. Also, we can conclude that ECG is generally more sensitive for the diagnosis of LVH in the male gender, regardless of its degree. In the male population, the $[(S + R) \times QRS]$ and Perugia scores showed higher sensitivity in our study sample.
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Table 1 – Characteristics of the study population by gender and degree of LVH

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mild LVH (n=321)</th>
<th>Moderate LVH (n=216)</th>
<th>Severe LVH (n=337)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.2±11.4</td>
<td>58.6±10.4</td>
<td>60.6±9.5</td>
</tr>
<tr>
<td>BS (m²)</td>
<td>1.8±0.1</td>
<td>1.6±0.1</td>
<td>1.6±0.1</td>
</tr>
<tr>
<td>BMI</td>
<td>27.2±6.3</td>
<td>28.4±5.3</td>
<td>25.6±3.4</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>109.3*</td>
<td>93.7*</td>
<td>153.4*</td>
</tr>
</tbody>
</table>

*Median; LVH = left ventricular hypertrophy; M = male; F = female; BS = body surface; BMI = body mass index; LVMI = left ventricular mass index
Table 2 – Comparison of the diagnostic sensitivity of ECG in the study of LVH between men and women, according with the increase in myocardial mass

<table>
<thead>
<tr>
<th>ECG criterion</th>
<th>[(S + R) X QRS]</th>
<th>Sokolow-Lyon voltage</th>
<th>Cornell duration</th>
<th>Romhilt-Estes</th>
<th>RaVL</th>
<th>Perugia</th>
<th>Strain pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Degree of LVH</strong></td>
<td>M % (CI)</td>
<td>F % (CI)</td>
<td>M % (CI)</td>
<td>F % (CI)</td>
<td>M % (CI)</td>
<td>F % (CI)</td>
<td>M % (CI)</td>
</tr>
<tr>
<td><strong>Mild LVH</strong></td>
<td>35.9 (26.0/46.8)</td>
<td>11.1 (7.4/15.9)</td>
<td>11.2 (5.5/19.6)</td>
<td>3.8 (1.7/7.2)</td>
<td>5.6 (1.8/12.6)</td>
<td>9.4 (6.0/13.9)</td>
<td>7.8 (3.2/15.5)</td>
</tr>
<tr>
<td><strong>Moderate LVH</strong></td>
<td>48.3 (35.2/61.6)</td>
<td>15.3 (10.1/22.0)</td>
<td>15.0 (7.1/26.5)</td>
<td>3.8 (1.4/8.1)</td>
<td>6.6 (1.8/16.2)</td>
<td>12.8 (8.0/19.1)</td>
<td>16.6 (8.2/28.5)</td>
</tr>
<tr>
<td><strong>Severe LVH</strong></td>
<td>76.0 (67.3/83.4)</td>
<td>40.0 (33.5/46.8)</td>
<td>31.6 (23.3/40.8)</td>
<td>19.3 (14.3/25.1)</td>
<td>11.9 (6.7/19.2)</td>
<td>38.2 (31.8/45.0)</td>
<td>20.5 (13.6/28.9)</td>
</tr>
</tbody>
</table>

ECG = electrocardiogram; LVH = left ventricular hypertrophy; M = male; F = female; CI = confidence interval