New Gender-Specific Partition Values for ECG Criteria of Left Ventricular Hypertrophy
Recalibration Against Cardiac MRI

Khaled Alfakih, Kevin Walters, Tim Jones, John Ridgway, Alistair S. Hall, Mohan Sivananthan

Abstract—ECG criteria for left ventricular hypertrophy (LVH) were mostly validated using left ventricular mass (LVM) as measured by M-mode echocardiography. LVM as measured by cardiac MRI has been demonstrated to be much more accurate and reproducible. We reevaluated the sensitivity and specificity of 4 ECG criteria of LVH against LVM as measured by cardiac MRI. Patients with systemic hypertension (n=288) and 60 normal volunteers had their LVM measured using a 1.5-Tesla MRI system. A 12-lead ECG was recorded, and 4 ECG criteria were evaluated: Sokolow-Lyon voltage, Cornell voltage, Cornell product, and Sokolow-Lyon product. Based on a cardiac MRI normal range, 39.9% of the hypertensive males and 36.7% of the hypertensive females had elevated LVM index. At a specificity of 95%, the Sokolow-Lyon product criterion had the highest sensitivity in females (26.2%), the Cornell criterion had the highest sensitivity in males (26.2%), and the Cornell product criteria had a relatively high sensitivity in both males and females (25.0% and 23.8%). Receiver operating characteristic curves showed the Cornell and Cornell product criteria to be superior for males whereas the Sokolow-Lyon product criterion was superior for females. Comparing the mean LVM index values of the subjects who were ECG LVH positive to the normal volunteers indicated that the ECG LVH criteria detect individuals with an LVM index substantially above the normal range. We have redefined the partition values for 4 different ECG LVH criteria, according to gender, and found that they detect subjects with markedly elevated LVM index. (Hypertension. 2004;44:175-179.)

Key Words: hypertrophy • remodeling • electrocardiography • imaging

Left ventricular hypertrophy (LVH) carries a substantial cardiovascular risk in patients with hypertension.1,2 The ECG is easy to acquire, readily available, and inexpensive. It is widely used in research and in clinical practice to detect LVH on the basis of several criteria that generally have high specificities and low sensitivities.3,4 The landmark Losartan Intervention For Endpoint reduction in hypertension (LIFE) study used 2 of these ECG criteria to diagnose LVH and confirm reduction of cardiovascular events with regression of LVH.5 The study initially used the product of QRS duration and Cornell voltage (RaVL+SV1), with an adjustment of 8 mV for females and a partition value of 2440 mV-ms (the Cornell product criterion).6,7 During the study, the adjustment for females was modified to 6 mV. Furthermore, the Sokolow-Lyon voltage criterion was introduced, as an alternative ECG LVH criterion, to increase recruitment.8

M-mode echocardiography can detect LVH accurately through measurement of left ventricular (LV) wall thickness. Left ventricular mass (LVM) as measured by M-mode echocardiography was used as the reference standard in most of the ECG LVH validation studies.9-13 However, it is neither accurate nor reproducible. It relies on LV wall thickness measurements, a mathematical formula, and geometric assumptions about the shape of the LV for the calculation of a 3D structure. The M-mode LV wall thickness measurements are cubed in the formula, which increases the standard deviations by a factor of 2 to 3 and, as a result, underestimates the prevalence of LVH in hypertensive cohorts.14 Furthermore, M-mode echocardiography consistently overestimates the LVM in the presence of LVH.15-17 Finally, the accuracy and the reproducibility of LVM, as measured by M-mode echocardiography, have been shown to be poor compared with direct measurement by 3D cardiac MRI.18 This implies that the ECG criteria have been validated against a variable reference standard.19

During the past decade, cardiac MRI has been established as the gold standard for the estimation of LVM. It provides a spatially defined 3D data set at multiple levels throughout the heart; hence, the measurement of LVM does not require geometric assumptions about the LV. The excellent contrast between blood and myocardial tissue together with the high spatial resolution mean that the endocardial and epicardial
contours are easily defined. LVM, as measured by cardiac MRI, has been validated in animal studies\(^\text{20,21}\) and has been demonstrated to be more accurate and reproducible than M-mode and 2D echocardiography measurements.\(^\text{18,22,23}\) As a result of the superior accuracy and reproducibility, fewer subjects are needed in research studies using cardiac MRI.\(^\text{24}\)

The aim of our study was to evaluate the Sokolow-Lyon voltage, Cornell sex-specific voltage, Sokolow-Lyon product, and Cornell product criteria against LVM index as measured by cardiac MRI in a large cohort of patients. We sought to establish gender-specific partition values for each criterion.\(^\text{25}\) We also sought to reevaluate the Romhilt-Estes score for LVH and P wave abnormalities\(^\text{26}\) against LVM index and to define the mean LVM index for individuals with positive ECG criteria for LVH.

### Methods

#### Patients and Volunteers

Patients with systemic hypertension (\(n=288\)) were recruited from the 24-hour BP and echocardiography departments. The majority of the patients were known to have a history of systemic hypertension and were attending the hospital for follow-up. The remaining patients were newly referred with the diagnosis of hypertension and were included in the study if they had 2 recorded resting systolic blood pressures (BPs) of \(\geq 160\) mm Hg, diastolic BP of \(\geq 100\) mm Hg, or both. Patients with a history of valvular heart disease, previous myocardial infarcts, arrhythmias, and left or right bundle branch block were excluded. A total of 60 normal volunteers (30 men and 30 women) were recruited to establish normal ranges for cardiac MRI assessment of LV volumes and mass.\(^\text{27}\) Written informed consent was obtained from all subjects, and the local ethics committee approved the study.

#### Imaging Methods

MRI studies were performed on a 1.5-Tesla Philips Intera CV MRI system equipped with Master gradients using a 5-element cardiac phased-array receiver coil and vectorcardiographic ECG synchronization; 10 to 14 slices were acquired during breath hold using a segmented K-space turbo-gradient echo pulse sequence (TR=8.8 ms, TE=5.2 ms, flip angle=35°).

Image analysis was performed off-line using commercially available analysis software (MASS, Medis, Leiden, the Netherlands). LVM was measured at end diastole, which was defined as the first phase in the cine sequence for each slice. For all data sets, one experienced observer manually traced the endocardial and epicardial contours of the LV. Two papillary muscles were outlined separately, excluded from the volume, and included in the mass (Figure). LVM was calculated as LVM=1.05 \times (epicardial volume-endocardial volume).

#### ECG

A standard 12-lead ECG was recorded at 25 mm/s and 1 mV/cm standardization, with a MAC 5000 resting ECG system (GE Medical Systems), on patients and volunteers on the same day as the MRI scanning. One observer, who was blinded to the MRI data, analyzed 4 ECG criteria: Sokolow-Lyon voltage,\(^\text{6}\) Cornell sex-specific voltage,\(^\text{28}\) Cornell product, and Sokolow-Lyon product.\(^\text{5}\) LVM was defined as a Sokolow-Lyon voltage amplitude of \((SV_1+RV_6)\geq 35\) mV, a Cornell voltage of \((RaVL+SV_3)\geq 28\) mV for men and \(\geq 20\) mV for women, and a Cornell product of \([(RaVL+SV_3)\times QRS duration] > 2440\) ms. There is no recognized partition value for the Sokolow-Lyon product \([(SV_1+RV_6)\times QRS duration]. For the patient group, the Romhilt-Estes score was calculated, using scores of 5 and 4 to diagnose LVH, and the P wave was defined as abnormal if the terminal negativity of the P wave in \(V_1\) was 1 mm or more.\(^\text{28}\)

#### Statistical Methods

The results were analyzed using STATA software (version 8, STATA Corporation). Means and SD were calculated for LVM indexed to body surface area (BSA). Elevated LVM index was defined for men and women separately, based on the mean LVM index for normal volunteers plus 2 SD.\(^\text{27}\)

The means and SD were calculated for each ECG criterion according to gender and LVH status. The need for gender-specific partition values in patients with and without LVH was evaluated using a 2-way ANOVA. We tested the sensitivity and specificity for the LVH criteria using existing partition values for the Sokolow-Lyon voltage, Cornell voltage, and Cornell product. For the Sokolow-Lyon product criterion, we established a partition value of 2940 mVms to give the same specificity as the Cornell product criterion. The results were decomposed to enable examination of the sensitivities and specificities according to gender using a \(\chi^2\) test. We also compared the sensitivities of the 4 criteria at a fixed specificity of 95%. Receiver operating characteristic (ROC) curves were used to compare the performance of the 4 criteria over a range of specificities. We calculated the specificity and sensitivity for the Romhilt-Estes score and for the P wave. We also compared the mean LVM index for the ECG positive versus the ECG negative individuals for each ECG criteria for men and women separately, and used a 2-sample \(t\) test to assess whether the means were significantly different for each of the ECG criteria.

#### Results

The mean±SD for age and BSA for the male patients was 55.1±11.7 years, 2.04±0.15 m\(^2\) (\(n=168\)) and for the female patients was 57.3±11.5 years, 1.78±0.17 m\(^2\) (\(n=120\)). The mean resting BP 160/92 mm Hg (\(n=288\)). Based on the cardiac MRI normal range,\(^\text{27}\) 39.9% of the hypertensive males had elevated LVM index (mean LVM index=93.4±18.3 g/m\(^2\), \(n=168\)) and 36.7% of the hypertensive females had elevated LVM index (mean LVM index=73.6±13.2 g/m\(^2\), \(n=120\)). The reproducibility of the LVM measurements was similar to previously published data with a SDD of 9.5 g and 10 g for intra- and interobserver variabilities.\(^\text{27}\)

Currently, only the Cornell criterion has gender-specific partition values. To examine the need for gender-specific partition values, means and standard deviations were calculated for each ECG criterion according to gender and LVH status based on cardiac MRI (Table 1). A 2-way ANOVA was performed. Within both the “LVH” and “No LVH” categories, males were found to have significantly \((P<0.01)\) higher means than females for all criteria, besides the Cornell
product criteria where the females had the significantly higher means.

We tested the sensitivity and specificity of the 4 criteria using established partition values: Sokolow-Lyon = 35 mV; Cornell-gender specific, male = 28 mV, female = 20 mV; Cornell product = 2440 mV⋅ms; and Sokolow-Lyon product = 2940 mV⋅ms. We retested the sensitivities and specificities according to gender (Table 2). To identify whether there were significant differences between the sexes in specificity and sensitivity, we used a χ² test. The probability values shown in Table 2 for the gender-specific results test the null hypothesis that the proportions are the same in males and females for both specificity and sensitivity (Table 2).

To make comparisons of sensitivities more meaningful, we compared the sensitivities of the 4 criteria at a fixed specificity of 95% (the most widely used in the literature).⁵,⁶,10 The sensitivities as well as the sex-specific partition values are shown in Table 3. The Sokolow-Lyon product criterion had the highest sensitivity for females (26.2%), whereas the Cornell product criteria had good sensitivity for both males and females (25.0% and 23.8%), at this level of specificity. We also compared the overall performance of the 4 ECG criteria by comparing the areas under the ROC curves. We only considered specificities above 80% because these represent the clinically relevant range. The ROC curves showed the Sokolow-Lyon product criterion to be superior in females, whereas the Cornell and the Cornell product criteria were superior for males at the higher specificities (Figure 1, available in an online supplement available at http://www.hypertensionaha.org). However, pair-wise tests comparing the area under the ROC curve for each criterion for each sex separately did not show any significant differences between any of the 4 criteria.

The sensitivity of the Romhilt-Estes score on the basis of a score of 5 was 19.8% with a specificity of 95.2%. Using the lower score of 4, the sensitivity improved to 50.9% but the specificity dropped to 73.8%. Similarly, we assessed the sensitivity of an abnormal P wave at detecting LVH and found it to be 49.1% with a specificity of 54.2%.

We calculated the mean LVM index for the ECG positive versus the ECG negative individuals for each ECG criteria for men and women separately (Figure II available online). A 2-sample t test comparing the ECG positive and the ECG negative individuals at the 5% level, after adjusting for multiple testing, demonstrated a significant difference between the means for the Sokolow-Lyon voltage and the Sokolow-Lyon product criteria in females and for the Cornell voltage criteria in males. There was a significant difference between the means for the Cornell product criteria in both males and females.

The mean LVM index for normal males was 77.8±9.1 g/m² and for normal females was 61.5±7.5 g/m².²⁷ The mean LVM index values for subjects with LVH on ECG, based on the 4 ECG criteria, were: males, Sokolow-Lyon = 106.6 g/m², Sokolow-Lyon product = 103.9 g/m², Cornell = 115.5 g/m², Cornell product = 116.0 g/m²; females, Sokolow-Lyon = 83.4 g/m², Sokolow-Lyon product = 84.7 g/m², Cornell = 80.7 g/m², Cornell product = 84.6 g/m². Comparing the mean LVM index values for subjects who were ECG LVH positive to the normal volunteers shows that in men the Cornell and Cornell product criteria detect subjects with LVM index 4 SD above normal, whereas in women, Sokolow-Lyon, Sokolow-Lyon product, and Cornell product criteria detect subjects with LVM index 3 SD above normal.

### Discussion

It has previously been demonstrated that gender differences in body size, obesity, and LVM do not completely account for

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### Table 1. Mean and SD Values for QRS Voltages and QRS Voltage-Duration Products According to Gender and LVH Status Based on Cardiac MRI

<table>
<thead>
<tr>
<th>ECG Criteria</th>
<th>No LVH on MRI</th>
<th>LVH on MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Sokolow, mV</td>
<td>25.2±8.0</td>
<td>22.7±6.4</td>
</tr>
<tr>
<td>Sokolow product, mV⋅ms</td>
<td>2390±820</td>
<td>1960±590</td>
</tr>
<tr>
<td>Cornell, mV</td>
<td>16.5±4.8</td>
<td>14.1±4.5</td>
</tr>
<tr>
<td>Cornell product, mV⋅ms</td>
<td>1560±520</td>
<td>1860±490</td>
</tr>
</tbody>
</table>

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### Table 2. Sensitivities and Specificities According to Established Partition Values Followed by Gender-Specific Sensitivities and Specificities

<table>
<thead>
<tr>
<th>ECG Criteria</th>
<th>Specificity</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sokolow</td>
<td>92.1%</td>
<td>28.7%</td>
</tr>
<tr>
<td>Sokolow product</td>
<td>91.4%</td>
<td>36.8%</td>
</tr>
<tr>
<td>Cornell</td>
<td>94.8%</td>
<td>21.3%</td>
</tr>
<tr>
<td>Cornell product</td>
<td>91.4%</td>
<td>31.1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ECG Criteria</th>
<th>Specificity</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sokolow</td>
<td>90.5%</td>
<td>94.2%</td>
</tr>
<tr>
<td>Sokolow product</td>
<td>82.0%</td>
<td>94.0%</td>
</tr>
<tr>
<td>Cornell</td>
<td>99.2%</td>
<td>89.3%</td>
</tr>
<tr>
<td>Cornell product</td>
<td>93.4%</td>
<td>89.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
<th>P</th>
<th>Male</th>
<th>Female</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sokolow</td>
<td>90.5%</td>
<td>94.2%</td>
<td>0.30</td>
<td>32.0%</td>
<td>23.3%</td>
</tr>
<tr>
<td>Sokolow product</td>
<td>82.0%</td>
<td>94.0%</td>
<td>&lt;0.01</td>
<td>53.1%</td>
<td>28.6%</td>
</tr>
<tr>
<td>Cornell</td>
<td>99.2%</td>
<td>89.3%</td>
<td>&lt;0.001</td>
<td>18.5%</td>
<td>25.6%</td>
</tr>
<tr>
<td>Cornell product</td>
<td>93.4%</td>
<td>89.0%</td>
<td>0.25</td>
<td>29.9%</td>
<td>33.3%</td>
</tr>
</tbody>
</table>

P values are for a χ² test to assess whether there are significant differences between the sexes in specificity and sensitivity for the various criteria.
the gender differences in QRS duration and voltage measurements. The results in Table 1 show that males have higher mean QRS voltage and QRS voltage duration product values than females, irrespective of LVH status, for all the ECG criteria except the Cornell product, where the 8 mV adjustment results in females having higher QRS voltage duration products. Furthermore, the sensitivity and specificity are different for all 4 criteria when assessed according to gender (Table 2). These differences suggest that gender-specific partitions ought to be used.

At a fixed specificity of 95% the Sokolow-Lyon product criterion had the highest sensitivity in females but was relatively insensitive for males whereas the Cornell product criterion had good sensitivity for both males and females (Table 3). The ROC curves confirmed the Sokolow-Lyon product criterion to be superior in females (Figure 1). In the LIFE study, the investigators used the Sokolow-Lyon voltage criterion with a partition value of 38 mV for both males and females, which would have resulted in lower sensitivity in women. Our results suggest a partition value for the Sokolow-Lyon voltage criterion of 34 mV for females. Furthermore, our results suggest that a gender-specific Sokolow-Lyon product criterion would have higher sensitivity in females and, hence, can enhance the identification and recruitment of eligible patients in such studies. We recommend the use of gender-specific partition values for ECG LVH criteria (Table 3).

Our patients were mostly receiving antihypertensive therapies, including both patients with mild and moderate to severe hypertension. We included patients with angina, but excluded patients with myocardial infarcts and valvular heart disease. Hence, our results cannot be extrapolated to patients with LVH secondary to valvular heart disease nor patients with LV remodeling following myocardial infarcts. The sensitivity of the ECG LVH criteria will vary depending on the cohort being studied. Molloy et al demonstrated sensitivity of 50% (at a level of specificity of 95%) for the Cornell product criterion compared with our equivalent value of 24.5%. They measured LVM at autopsy in cases with differing cardiac pathology, compared with our cohort of patients with treated hypertension. Moreover, the sensitivity of the ECG LVH criteria will vary depending on the severity of hypertension and prevalence of LVH in the cohort being studied. Okin et al demonstrated higher sensitivities for ECG LVH criteria in a subgroup of patients with LVM index higher than the median value (>152.8 g/m²) for the cohort that they studied. Furthermore, Okin et al found both Sokolow-Lyon voltage and Sokolow-Lyon product criteria to have higher sensitivities (43% and 45%) than Cornell voltage and Cornell product criteria (28% and 37%) in a cohort of 389 subjects, most with hypertension, but also included 69 patients with regurgitant valvular heart disease. M-mode echocardiography was used to measure LVM, and the results were expressed for the whole cohort and not according to gender.

The comparison of the mean LVM index between the ECG positive and ECG negative individuals for each of the criteria illustrates that the ECG criteria of LVH detect a group of patients with hypertension that have a significantly elevated LVM index. This is clinically relevant as there is a continuous relationship between LVM index and cardiovascular risk. Schillaci et al followed-up a large cohort of subjects (n=1925) with essential hypertension for 4 years. LVM was measured using M-mode echocardiography, and the prevalence of elevated LVM in the cohort was 30.5%. The cohort was divided into 5 gender-specific quintiles of progressively higher LVM index. The relative risk of a cardiovascular event increased progressively with LVM index, even after adjustment for cardiovascular risk factors, including 24-hour ambulatory blood pressure. Furthermore, the LIFE study, where there was a high prevalence of ECG LVH positive patients, confirmed that LVH regression results in improved outcomes, independent of BP reduction. Our results suggest that the ECG LVH positive patients in the LIFE study are likely to have had significantly elevated LVM.

**Perspectives**

ECG criteria are known to have high specificity for detecting LVH. Furthermore, we have shown that the presence of ECG criteria of LVH detects individuals who have substantially elevated LVM index and an assumed increased cardiovascular risk. The LIFE study provided evidence of the prognostic benefit of LVM regression. However, demonstration of LVM regression using ECG criteria of LVH in the LIFE study was only possible because it was a very large cohort. Demonstration of LVM regression using echocardiographic methods also requires relatively large cohorts of patients because of the high observer and interstudy variability. Cardiac MRI has become the technique of choice for precise measurements of LVM. This 3D technique, with excellent definition of endocardial and epicardial borders, is highly reproducible, which means that a much smaller sample size is needed to detect LVM regression in clinical trials. Furthermore, the serial monitoring of an individual patient to detect changes in LVM can be done with much higher certainty. The acquisition time of the cardiac MRI scan for LV volumes and mass using the most recent techniques can

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**TABLE 3. Sensitivities of the 4 ECG Criteria and the Male/Female Partition Values at 95% Specificity**

<table>
<thead>
<tr>
<th>ECG Criteria</th>
<th>Combined Sensitivity %</th>
<th>Male Sensitivity %</th>
<th>Female Sensitivity %</th>
<th>Male Partition Value</th>
<th>Female Partition Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sokolow</td>
<td>20.3</td>
<td>18.5</td>
<td>23.3</td>
<td>&gt;38</td>
<td>&gt;34</td>
</tr>
<tr>
<td>Sokolow product</td>
<td>17.0</td>
<td>10.9</td>
<td>26.2</td>
<td>&gt;4032</td>
<td>&gt;2970</td>
</tr>
<tr>
<td>Cornell</td>
<td>22.2</td>
<td>26.2</td>
<td>16.3</td>
<td>&gt;25</td>
<td>&gt;21</td>
</tr>
<tr>
<td>Cornell product</td>
<td>24.5</td>
<td>25.0</td>
<td>23.8</td>
<td>&gt;2592</td>
<td>&gt;2610</td>
</tr>
</tbody>
</table>
be as short as 3 minutes. The LV volumes analysis in this study was done manually and took, on average, 15 minutes per patient. However, automated contour detection for LV volume analysis software continues to improve and in the near future the speed and accuracy of cardiac MRI should offset any cost differential with echocardiography.

Conclusion
We have provided new gender-specific partition values for the 4 ECG LVH criteria, recalibrated against a precise LVM index, as measured by cardiac MRI. We have also shown that ECG LVH criteria do denote patients with a substantially elevated LVM index.

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References
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