Gender-Adjustment and Cutoff Values of Cornell Product in Hypertensive Japanese Patients

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Summary

In the Japanese population, the electrocardiographic (ECG) Cornell voltage and product predict cardiovascular events at lower values (Cornell voltage of 2.04 mV in males and 1.71 mV in females, and Cornell product of 158.7 mV × msec) than in the guidelines (2.8 mV, 2.0 mV, and 244 mV × msec, respectively). We evaluated the ECG criteria for left ventricular hypertrophy (LVH) corresponding to echocardiographic LVH (Echo-LVH) in Japanese patients.

We reviewed data on 345 consecutive hypertensive patients who underwent echocardiography, and evaluated the Cornell voltage (S in leads V3 + R in leads aVL), Cornell product [(Cornell voltage + 0.6 mV for females) × QRS duration], and left ventricular mass index (LVMI) (Echo-LVH: LVMI ≥ 116 g/m² in males and ≥ 96 g/m² in females).

The mean age was 63.8 ± 12.5 years (174 males/172 females). Echo-LVH was found in 22.7% of males and 37.2% of females. The equations for estimating LVMI from the Cornell voltage were (1) LVMI = 14.5 × Cornell voltage + 78.9 for males and (2) LVMI = 21.5 × Cornell voltage + 61.5 for females. The Cornell voltage corresponding to Echo-LVH was 2.6 mV in males and 1.6 mV in females, which were below the guideline levels and close to the values indicating cardiovascular risk. The equation for estimating LVMI from the Cornell product was LVMI = 0.15 × Cornell product + 68.8. The Cornell product corresponding to Echo-LVH was 170 mV × msec (sensitivity: 0.730, specificity: 0.601), which was also close to the cardiovascular risk level.

Cornell voltage and product values indicating Echo-LVH are lower than those in the current guidelines and closer to the cardiovascular risk levels.

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Key words: Cornell voltage, Sokolow-Lyon voltage, Electrocardiogram, Left ventricular hypertrophy

Subjects with left ventricular hypertrophy (LVH) have an increased risk of cardiovascular events and stroke.1-3) The 2014 Japanese Society of Hypertension (JSH) guidelines recommend evaluation of the Sokolow-Lyon voltage, Cornell voltage, and Cornell product.4) In our previous study performed in a general Japanese population,5) subjects with these ECG criteria for LVH (ECG-LVH) had an increased risk of cardiovascular events and stroke, but the values of the Cornell voltage, Cornell product, and Sokolow-Lyon voltage at which cardiovascular events increased were below the cutoff levels in western populations5,8) and in the 2014 JSH guidelines.9) A cohort study performed in Singapore also suggested that Asian populations might have different ECG-LVH cutoff levels for detecting anatomical LVH,9) and the ECG-LVH was associated with an increased risk of cardiovascular events.6)

In the present study, we evaluated whether gender adjustment of the Cornell product was appropriate in hypertensive Japanese patients, and also determined the level of ECG-LVH corresponding to anatomical (echocardiographic) LVH.

Methods

Subjects: We reviewed echocardiography data obtained when screening consecutive hypertensive outpatients for target organ damage at Sano Kosei General Hospital between January 2010 and June 2014. There were 345 sets of echocardiographic and ECG data, including annual follow-up data. The exclusion criteria were as follows: (1) significant arrhythmia, (2) complete left or right bundle branch block, (3) were unable to obtain or unclear echocardiographic images, (4) a history of ischemic heart disease, and (5) asynergy of left ventricular wall motion.

ECG measurement and interpretation: The ECG was recorded using an automated 12-lead ECG monitor (Fukuda Denshi, Inc., Tokyo, Japan). This monitor auto-
matically measured the QRS duration, S in leads V1, and R in lead V5 (Sokolow-Lyon criteria), while R in lead aVL, and S in lead V3 (i.e., Cornell voltage) were measured manually. Then the Cornell product was calculated as Cornell voltage (+ 0.6 mV in females) × QRS duration. A Cornell voltage ≥ 2.8 mV in males and ≥ 2.0 mV in females, Cornell product ≥ 244 mV × msec, or Sokolow-Lyon voltage ≥ 3.5 mV were defined as diagnosing ECG-LVH in the 2014 JSH Guidelines for the Management of Hypertension, while a Cornell product ≥ 244 mV × msec and Sokolow-Lyon voltage ≥ 3.8 mV were used to diagnose ECG-LVH in the Losartan Intervention For Endpoint Reduction in Hypertension Study.

**Echocardiography:** The first author performed most of the echocardiography examinations using an Altida (Toshiba, Japan) with a 3.5-MHz transducer. The absence of apparent asynery of LV wall motion was confirmed in all patients. Two-dimensional B-mode images were recorded according to the guidelines of the American Society of Echocardiology.

Then LV mass was calculated by the following formula: 0.832 × [(IVS + LVID + PW) - (LVID)^2] × 0.6, where IVSd is the diastolic interventricular septal diameter, LVIDd is the diastolic LV dimension, and PWd is the diastolic posterior wall diameter. LVMI was calculated as LV mass divided by body surface area. The mean inter-observer difference of LVMI was 6.6 ± 19.5 g/m².

**Informed consent:** The institutional review board of Sano Kosei General Hospital approved this study. We did not obtain written informed consent because this was a retrospective analysis of routine clinical data.

**Statistical analysis:** Results are shown as the mean ± SD for continuous variables or as percentages for categorical variables. Relations between electrocardiographic measures of LVH and LVMI were evaluated by calculating Pearson’s correlation coefficients. The predictive value of ECG-LVH for echocardiographic LVH (Echo-LVH) was determined by receiver operating characteristics (ROC) analysis with calculation of the area under the curve (AUC). SPSS statistical software (version 18.0, Chicago, IL, USA) was used for all analyses and P < 0.05 was considered to be statistically significant.

**Results**

**Subjects:** The characteristics of the subjects (n = 346) are shown in the Table. The mean age was 63.8 ± 12.5 years (174 males/172 females). There were 39 males (22.7%) and 64 females (37.2%) with Echo-LVH.

**Relationship of the Cornell voltage to LVMI in males and females:** Scatter plots of the relation between the Cornell voltage and LVMI are shown in Figures 1A (males), 1B (females). According to linear regression analysis, the equations for estimating LVMI from the Cornell voltage are as follows: (1) LVMI = 12.2 × Cornell voltage + 78.9 in males and (2) LVMI = 21.5 × Cornell voltage + 61.5 in females. The voltage corresponding to Echo-LVH (LVMI ≥ 116 g/m² in males and ≥ 96 g/m² in females) was 2.6 mV in males and 1.6 mV in females. Sensitivity and specificity at different cutoff Cornell voltages are shown in Figures 2A (males), 2B (females). The cutoff levels listed in the 2014 guidelines of the JSH (2.8 mV in males and 2.0 mV in females) showed high sensitivity, but very low specificity.

**Relationship of the Sokolow-Lyon voltage to LVMI in males and females:** Scatter plots of the relation between the Sokolow-Lyon voltage and LVMI are shown in Figure 1C (males) and 1D (females). According to linear regression analysis, the equations for estimating LVMI from the Sokolow-Lyon voltage are as follows: (1) LVMI = 12.2 × Sokolow-Lyon voltage + 70.0 in males and (2) LVMI = 13.1 × Sokolow-Lyon voltage + 59.7 in females. The voltage corresponding to Echo-LVH was 3.8 mV in males and 2.8 mV in females. Although cardiovascular risk levels of the Sokolow-Lyon voltage (i.e., 3.0 mV) were lower than the 2014 guideline levels of the JSH (i.e., 3.5 mV), these relationships to the Sokolow-Lyon voltage corresponding to Echo-LVH were inconsistent between males and fe-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
<th>Reference</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>63.8 ± 12.5</td>
<td></td>
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<tr>
<td>Male, %</td>
<td>50.3</td>
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<tr>
<td>Body mass index, g/m²</td>
<td>24.6 ± 4.2</td>
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<tr>
<td>Systolic blood pressure, mmHg</td>
<td>145.5 ± 23.7</td>
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<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>85.0 ± 14.8</td>
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<td>Pulse rate, beat/minute</td>
<td>72.2 ± 11.9</td>
<td></td>
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</tr>
<tr>
<td>Antihypertensive drug use, %</td>
<td>69.3</td>
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<tr>
<td>Calcium channel blockers, %</td>
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<tr>
<td>Beta blockers, %</td>
<td>12.2</td>
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<tr>
<td>Alpha blockers, %</td>
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<tr>
<td>Statin use, %</td>
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Data are shown as mean ± standard deviation or percentage.
males.

**Gender adjustment of the Cornell product:** AUCs obtained for detecting Echo-LVH with different gender-adjusted values of the Cornell product are shown in Figure 3. The AUC for the unadjusted Cornell product was 0.690 and it increased to 0.738 for the gender-adjusted Cornell product (0.6 mV added to Cornell voltage in females). There was a small increase of the AUC using adjusted values of 0.6-0.8 mV.

**Relationship of the Cornell product to LVMI:** Based on the scatter plot in Figure 4, the equation for estimating LVMI from the gender-adjusted Cornell product is as follows: LVMI = 0.15 × Cornell product + 68.8. According to ROC analysis (Figure 5), the optimum value of the Cornell product for predicting Echo-LVH was 170 mV × msec (sensitivity: 0.730, specificity: 0.601).

**Discussion**

The present study showed that the Cornell voltage and product values in the current 2014 JSH guidelines (a Cornell voltage of 2.8 mV in males and 2.0 mV in females or a Cornell product of 244 mV × msec) have a high specificity for detecting Echo-LVH in hypertensive Japanese patients, but have a very low sensitivity. The ECG-LVH values corresponding to Echo-LVH (anatomical LVH) in the present study were a Cornell voltage of 2.6 and 1.6 mV (i.e., an LVMI of 116 g/m² for males and 96 g/m² for females, respectively), which were lower than the values in the guidelines and closer to those reported in-
Figure 2. A: Receiver operating characteristics analysis curve of the Cornell voltage for detecting Echo-LVH (LVMI > 116 g/m²) in males. B: Receiver operating characteristics analysis curve of the Cornell voltage for detecting Echo-LVH (LVMI > 116 g/m²) in females.

Figure 3. Area under the curve (AUC) for detecting Echo-LVH with the Cornell product using different gender adjustment values. Echo-LVH was defined as LVMI > 116 g/m² in males and LVMI > 96 g/m² in females.

Figure 4. Scatter plot of the Cornell product versus LVMI. The regression line was LVMI = 0.15 × (Cornell product) + 68.8, r = 0.409, P < 0.001. A Cornell product of 159 mV × msec (cardiovascular risk) estimates an LVMI of 93 g/m² and a product of 244 mV × msec (guideline value) estimates an LVMI of 105 g/m².

dicate an increased risk of cardiovascular events and stroke (i.e., a Cornell voltage of 2.04 mV in males and 1.71 mV in females or a Cornell product of 158.7 mV × msec). Gender adjustment of the Cornell product (by adding 0.6 mV to the Cornell voltage in females) improved detection of Echo-LVH in our study population of hypertensive Japanese patients. Our findings suggested that the cutoff values for ECG-LVH should be lower than those in the current Japanese guidelines.

A previous meta-analysis has shown that ECG-LVH is a poor predictor of Echo-LVH (sensitivity of 10.5-21% and specificity of 89-99%).11 and similar results were obtained in a study that evaluated LVH using cardiac MRI.12 The results of this study performed in Japan supported these reports from western countries. On the other hand, racial differences of Cornell values were reported between white and African American populations, or between white and Singaporean populations. Additionally, the Cornell voltages detecting Echo-LVH in Korean patients...
(2.0 mV in males and 1.6 mV in females) were similar to those indicating cardiovascular risk in the general Japanese population. To our knowledge, this was the first study, in a Japanese population, that showed the levels of Cornell voltages and product to estimated anatomical LVH.

It was reported that ECG-LVH predicts future cardiovascular events without predicting Echo-LVH (anatomical LVH), suggesting that these two types of LVH might be slightly different risk markers. Because LVH involves both enlargement of cardiomyocytes and interstitial fibrosis, electronic and anatomical hypertrophy would not necessarily be identical. Therefore, it might be better to set cut-off values for ECG-LVH so as to detect cardiovascular risk, rather than set values corresponding to anatomical LVH.

Limitations: This study was performed at a single center and most of the echocardiography studies were performed by the first author. Accordingly, the results should be confirmed by a multicenter study using cardiac CT or MRI. Additionally, LVMI could be affected by age, gender, body mass index, systolic blood pressure, antihypertensive drug use, and alcohol intake.

Conclusion

The sensitivity of the Cornell voltage and Cornell product values recommended by the 2014 JSH guidelines was very low in hypertensive Japanese patients. Thus, these ECG-LVH criteria did not correspond to Echo-LVH. In addition, Cornell voltage and product values indicating cardiovascular risk were lower than those in the JSH guidelines or those reported in western populations, suggesting that lower Cornell cutoff values for ECG-LVH may be more appropriate in Japanese patients.

Disclosures

Conflicts of interest: None.

References
