Evaluation of Hypertensive Cardiac Abnormalities
Using the Cornell Product

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Background  The Cornell product (CP) improved identification of left ventricular hypertrophy (LVH) in the LIFE study, although its clinical significance is still unknown in Japanese hypertensive (HT) patients.

Methods and Results  A standard 12-lead ECG was recorded in 265 HT and 363 normotensive cases (N). All ECGs were digitized, and a simple product was calculated by multiplying the Cornell voltage (CV) by the QRS duration. In 147 of the 265 HT cases, the standard 12-lead ECG and transthoracic Doppler echocardiography were examined in the same period. The mean value of CP increased in the following order: 1.426±673 mm·ms in N, 1.989±900 mm·ms in HT with treatment, 2.137±976 mm·ms in HT without treatment. The correlation with left ventricular mass index (LVMI) measured by echocardiography was improved by CP with the simple CV. With use of a partition of 2,440 mm·ms in CP, LVMI and relative wall thickness were significantly higher in HT with ≥2,440 mm·ms of CP compared with <2,440 mm·ms. Early diastolic wave in tissue Doppler imaging was significantly lower in HT with ≥2,440 mm·ms of CP compared with <2,440 mm·ms.

Conclusion  The Cornell product is a useful ECG marker, reflecting not only left ventricular (LV) mass but also LV geometry and diastolic function in Japanese HT patients. (Circ J 2007; 71: 731–735)

Key Words:  Cornell product; Hypertension; Left ventricular hypertrophy

As described in epidemiological data and large-scale clinical trial results, the incidence of cardiovascular complications is higher in hypertensive (HT) patients than in those with normal blood pressure and rigorous blood pressure management can prevent them.1–5 Further, it is well known that the complication of left ventricular hypertrophy (LVH) creates a higher risk of cardiovascular complications6–10 which is why monitoring and management of LVH are crucial in HT patients. Electrocardiography or echocardiography is generally used for detection of LVH, and although echocardiography has higher sensitivity, ECG is preferable from the perspective of its convenient operation and cost effectiveness. In the LIFE study, the Cornell product (CP) was used for the diagnosis of LVH, because it is one of the ECG-LVH criteria, and because of its usefulness11–13 the CP was adopted as a diagnostic criteria of ECG-LVH in the 2003 European Society of Hypertension-European Society of Cardiology Guideline.14 However, the usefulness of the CP for the care of HT patients in Japan has not been fully evaluated.

The purpose of this study was to examine the role of the CP in detecting cardiac abnormalities, including LVH, in Japanese patients with essential HT.

Methods

The study group comprised 265 outpatients with essential HT (male:female 174:91; age range: 30–87, average: 61.1±11 years) maintaining normal left ventricular (LV) systolic function (≥50% of the LV systolic ejection fraction) and having no LV dilatation (<55 mm of LV end-diastolic dimension). As the control group 363 normotensive outpatients (male:female 206:157, age range: 11–87, average: 50±11 years) were selected. Of the HT patients 230 (87%) had been administered antihypertensive medication, and 35 cases (13%) were untreated. The standard 12-lead ECG was recorded as a routine examination in all cases. In 147 of the 265 HT cases (male:female 102:45, age range: 30–87, average: 59±11 years), the standard 12-lead ECG and transthoracic Doppler-echocardiography were performed in the same period to evaluate cardiac condition. In both groups, those having any type of organic structural heart disease, such as myocardial infarction, valvular heart disease or cardiac myopathy, or showing any ECG abnormalities, such as bundle branch block, Wolff-Parkinson-White syndrome, abnormal Q or atrial fibrillation, were excluded.

In accordance with the previous reports11–13 the CP was calculated using the standard 12-lead ECG. The CP value is the simple product of QRS voltage and duration. The simple voltage–duration product was calculated by multiplying the Cornell voltage (CV; sum of the amplitude of R wave in lead aVL and the amplitude of S wave in lead V1) by QRS duration. Therefore, the formula for CP= (RaVL + SV3) × QRS duration. The unit of CP is mm·ms based on the description of the QRS amplitude as mm and duration as ms. The CV(RaVL+ SV3:mm) and the Sokolow-Lyon voltage (SLV=SV1+ RV5), which have been widely used for detecting LVH, were also calculated, aiming to determine the usefulness of the CP. All ECGs were digitized, and QRS duration was measured automatically to the nearest 2 ms and QRS amplitude to the nearest 5 mV. In accordance with the LIFE study11–15 and the 2003 European Society of Hypertension-European Society of Cardiology Guideline14 the diagnostic criterion for LVH with CP was determined as above 2,440 mm·ms.
LV mass (LVM) was calculated as $LVM = 1.04 [(LVID + PWT + IVST)^3 - LVID^3] \times 0.8 + 0.6$, based on the transthoracic echocardiography results, and was described by the LVM index (LVMI g/m²). LVID, LVPWT, and IVST represented the LV internal dimension (cm), LV posterior wall thickness (cm), and interventricular septal thickness (cm), respectively, when all determinations were conducted at end diastole. In regard to echocardiography indices other than LVM, the LV end-diastolic dimension (LVDd) and the relative wall thickness (RWT) were analysed as indices of LV morphology, and the mid-wall fractional shortening (MFS, %) and the LV ejection fraction (LVEF, %) were examined as indices of LV systolic function. In regard to the indices representing LV diastolic function, the ratio of the peak early transmitral flow velocity to the peak atrial transmitral flow velocity (E/A), the deceleration time (DT) of the E-wave, and the LV isovolumic relaxation time (IRT) in the LV filling flow determined with pulse Doppler method were analysed, as well as the peak early diastolic myocardial velocity (Em) using tissue Doppler imaging.

Table 1 Correlation Between the CV, CP, and SLV and Each Echocardiography Index

<table>
<thead>
<tr>
<th>Echo index</th>
<th>R value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVMI</td>
<td>0.536</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVDd</td>
<td>0.230</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RWT</td>
<td>0.397</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MFS</td>
<td>-0.036</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEF</td>
<td>-0.065</td>
<td>0.4352</td>
</tr>
<tr>
<td>E/A</td>
<td>-0.110</td>
<td>0.1851</td>
</tr>
<tr>
<td>DT</td>
<td>0.042</td>
<td>0.6143</td>
</tr>
<tr>
<td>IRT</td>
<td>0.221</td>
<td>0.0070</td>
</tr>
<tr>
<td>Em</td>
<td>-0.268</td>
<td>0.0013</td>
</tr>
</tbody>
</table>

CV, Cornell voltage; CP, Cornell product; SLV, Sokolow-Lyon voltage; LVMI, left ventricular mass index; LVDd, left ventricular diastolic dimension; RWT, relative wall thickness; MFS, mid-wall fractional shortening; LVEF, left ventricular ejection fraction; E/A, early transmitral flow velocity to the peak atrial transmitral flow velocity; DT, deceleration time; IRT, isovolumic relaxation time; Em, early diastolic myocardial velocity.

Results

CP and CV, and the SLV Among the Normotensive Group, Treated HT Group, and Non-Treated HT Group

The CV, CP, and SLV gradually increased in the normotensive group (CV: 13.4±5.9 mm, CP: 1,427±674 mm·ms, SLV: 25.5±7.6 mm), treated HT group (CV: 18.8±7.2 mm, CP: 1,990±900 mm·ms, SLV: 29.4±9.1 mm), and non-treated HT group (CV: 19.6±7.9 mm, CP: 2,138±976 mm·ms, SLV: 32.2±11.1 mm) in that order. In the comparison among the 3 groups, both the treated and the non-treated HT groups showed significantly higher CV, CP, and SLV compared with the normotensive group, whereas there was no significant difference between the treated and the non-treated HT groups (Fig 1). The systolic and diastolic blood pressures (SBP and DBP) in the non-treated HT group were significantly higher than in the treated HT group.
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(SBP: 160.3±17.0 vs 137.8±8.7 mmHg, p<0.05; DBP: 94.9±8.0 vs 79.0±7.8 mmHg, p<0.05).

Relationships Between CP, CV, the SLV and Each Echocardiography Index
The CP and CV showed significant positive correlations with LVMI, LVDd, RWT, and IRT, and significant negative correlation with Em, and had no significant correlation with the other echocardiographic indices (Table 1). In respect to the significant correlation with LVMI, RWT, and LVDd, LVMI showed the highest correlation with CP and CV, both above 0.5. In respect to the correlation coefficient with LVMI, CV was 0.536 and CP was higher at 0.545 (Fig 2).

The SLV also showed significant positive correlations with LVMI and LVDd; however, it had no significant correlation with the other echocardiographic indices (Table 1). In respect to the correlation coefficient with LVMI, SLV was lower (0.463) compared with CV and CP (Fig 2).

Clinical Significance of Using CP ≥2,440 mm·ms as ECG-LVH Criterion
In the comparison with the CP ≥2,440 mm·ms group and the <2,440 mm·ms group, LVMI was significantly high at

![Fig 2. Correlation between the Cornell voltage (CV), Cornell product (CP), and Sokolow-Lyon voltage (SLV) and left ventricular mass index (LVMI).](image)

![Fig 3. Difference in the left ventricular mass index (LVMI) between hypertensive patients with and without ECG-left ventricular hypertrophy (LVH) determined by the Cornell product.](image)

![Fig 4. Difference in the relative wall thickness (RWT) between hypertensive patients with and without ECG-left ventricular hypertrophy (LVH) determined by the Cornell product.](image)

![Fig 5. Difference in the early diastolic wave between hypertensive patients with and without ECG-left ventricular hypertrophy (LVH) determined by the Cornell product.](image)
LV diastolic function, the 0.05 (Fig 4). In accordance with the Em value representing 0.39±0.07 vs 0.36±0.05 (Fig 4). In accordance with the Em value representing LV diastolic function, the >2,440 mm·ms group showed 9.1±2.4 cm/s, which was significantly low compared with the 10.9±5.7 cm/s in the <2,440 mm·ms group (Fig 5). However, there were no significant differences between both groups in the other echocardiography indices.

Discussion
The CP was proposed as a diagnostic criteria of ECG-LVH in the LIFE study11–13 and in the 2003 European Society of Hypertension-European Society of Cardiology Guideline14. Its usefulness however, for the care of Japanese HT patients, to the best of our knowledge, has not been sufficiently evaluated. Because it is well-known that the specificity and sensitivity to the diagnostic criteria of ECG-LVH are affected by race17, it is crucial to the clinical significance in Japanese HT patients that the mechanism of CP determining cardiac abnormalities accompanied by high pressure, such as LVH, is studied.

In this study, the CP showed significant positive correlation with LVM, RWT, LV dimensions, and the LV isovolumic relaxation time, and significant negative correlation with the peak early diastolic myocardial velocity, as did the CV. The SLV, which is widely used for detection of LVH in Japanese HT patients, also showed significant positive correlation with LVM and LV dimensions, but had no significant correlation with RWT and the indices of LV diastolic function, such as the LV isovolumic relaxation time and the peak early diastolic myocardial velocity. In the correlation study with LVM, the CP had a 0.545 correlation coefficient value, which was higher than that of the CV at 0.536 and the SLV at 0.462. In a similar study conducted by Okin et al18 who proposed that the CP and the CV showed a significant positive correlation with LVM calculated from echocardiography results. The correlation coefficient value was increased to 0.56 with the CP compared with a value of 0.52 derived from using the CV. Those findings were quite similar to the present result. Consequently, it is suggested that the CP could be a trigger that induced a significant suppressive effect on cardiovascular events in the losartan group. The CP decreasing ratio was significant in the losartan group and atenolol group, showing a trend toward increasing RWT. In other words, the CP represents not only LVM, but also is a candidate clinical marker of morphological change in the LV. The LIFE echocardiographic substudy shown that RWT increased stepwise from normotensives to employed HTs to LIFE patients20.

For all the cardiac functional indices, except Em, there were no significant differences between the CP ≥2,440 mm·ms group and the <2,440 mm·ms group. However, in regard to Em, the CP ≥2,440 mm·ms group showed a significantly low value than the <2,440 mm·ms group, which suggested that the CP ≥2,440 mm·ms group possibly had impaired LV diastolic function compared with the <2,440 mm·ms group. Because it has been reported that the Em has a significant negative correlation with tau, representing LV relaxation abnormality in LV diastolic function, and is not affected by preload21, it could well represent the diastolic functional impairment accompanying HT-LVH. It is suggested that the CP could represent diastolic functional abnormality as well. It is important to evaluate LV diastolic function because it occurs commonly, even without LV systolic dysfunction, in HT patients22.

The present results suggest that the CP is a good ECG marker of LVM and also has the possibility of being a surrogate marker for cardiac abnormalities induced by HT, such as LV morphological change and LV diastolic dysfunction. For these reasons, the CP is considered a useful ECG marker for the care of HT patients.

In the present study, the CP values gradually increased from normal pressure group, the treated HT group to the non-treated HT, in that order, which indicated that the CP performed as a surrogate marker for cardiac abnormalities, including LVH.

In the LIFE study, the time course of the CP was also examined in relation to medical treatment, and it was reported that even though the same level of blood pressure reduction was achieved in the losartan group and atenolol group, the CP decreasing ratio was significant in the losartan group, ranging from 6 months to 5 years after medical treatment had been initiated23. It could be suggested that the efficacy of regression of hypertrophy was significant and could be a trigger that induced a significant suppressive effect on cardiovascular events in the losartan group. The background to this idea is that it is well known that a cardiovascular event suppressive effect is observed in the regression of LVH with antihypertension treatment24 and in the follow-up examination in the LIFE study, it was suggested that the CP time course in therapy reflected the change in LVM on echocardiography25. According to those findings, the CP could be the ECG marker that can represent the change in LVM with antihypertension treatment as well as for detecting LVH induced by HT.

As 87% of the present HT cases were being treated, the influence of drugs on the results would be crucial. According to the result reported by Okin et al18 for the correlation between the CP and LVM calculated from echocardiography, their findings were quite similar to ours, and the time

course of the CP value reflected well the change in LVM on echocardiography in the LIFE study. Therefore, regardless of therapy, the CP is considered a good ECG marker of LVM. As the blood pressure influence on the CP was not examined fully in this study, further examination with many cases is required.

In conclusion, we suggest that the CP is an ECG marker that well represents LVM, as well as LV morphological change, and the Em derived from tissue Doppler imaging which represents LV diastolic function in Japanese HT patients. Therefore, the CP is a possible surrogate marker of cardiac abnormalities, such as Lvh, induced by hypertension, and is useful for the care of HT patients.

References