Different Effects of Temocapril and Cadralazine on Electrocardiographic Voltages and Left Ventricular Mass in Patients with Essential Hypertension

Shin Tomita, MD, Masanobu Takata, MD, Kotaro Yasumoto, MD, Fumihiro Tomoda, MD, Hitoshi Ueno, MD, and Hiroshi Inoue, MD

SUMMARY

To assess whether electrocardiographic variables are useful to detect the regression of left ventricular (LV) mass after long-term antihypertensive treatment, we related electrocardiographic voltages to echocardiographic variables before and after treatment with an ACE inhibitor, temocapril (TEM), or direct vasodilator, cadralazine (CAD). Twenty-one patients with essential hypertension were treated with either TEM (n = 11) or CAD (n = 10) for one year. LV mass index (LVMİ) by echocardiography and Sokolow-Lyon voltage (SV₁ + RV₆), Cornell voltage (RaV₁ + SV₆) and RV₁ + RV₆ by standard 12-lead electrocardiographic voltages were determined before and after treatment. Both drugs decreased blood pressure to the same extent. Both Sokolow-Lyon voltage and RV₁ + RV₆ tended to decrease in the ACE group (40.0 ± 9.4 to 37.2 ± 9.4 mm and 44.7 ± 13.5 to 41.7 ± 11.7 mm, respectively, N.S.), but not in the CAD group (38.4 ± 6.8 to 39.7 ± 7.7 mm and 42.9 ± 10.4 to 46.8 ± 11.2 mm, respectively, N.S.). LVMI decreased in the ACE group (24 ± 22 g/m²), whereas it increased in the CAD group (37 ± 27 g/m², p < 0.01). Change in LVMI was correlated with the changes in RV₁ + RV₆ and Sokolow-Lyon voltage (r = 0.73, p < 0.01 and r = 0.70, p < 0.01, respectively), but not with that in Cornell voltage. These results indicated that the changes in voltage criteria of RV₁ + RV₆ and Sokolow-Lyon are useful to assess the change in LVM after antihypertensive treatment in patients with essential hypertension although voltage variables in electrocardiogram were not sensitive to detect changes in LVMI. (Jpn Heart J 1999; 40: 55–63)

Key words: Left ventricular hypertrophy, Essential hypertension, Electrocardiogram, Echocardiography, ACE inhibitor, Direct vasodilator

From the Second Department of Internal Medicine, Toyama Medical and Pharmaceutical University, Toyama, Japan.
Address for correspondence: Masanobu Takata, MD, The Second Department of Internal Medicine, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama, 930-0194, Japan.
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Echocardiographically determined left ventricular (LV) mass is a major risk factor and a powerful independent predictor of cardiovascular events in patients with essential hypertension. It is crucial to regress LV hypertrophy seen in essential hypertension, since several investigators demonstrated that improvement of cardiovascular morbidity and mortality is associated with regression of LV hypertrophy. However, different antihypertensive drugs have different effects on LV mass (LVM) in patients with hypertension. Moreover, animal studies have indicated that a direct vasodilator such as hydralazine worsens LV hypertrophy in spontaneous hypertensive rats in spite of reduction in blood pressure.

Standard 12-lead electrocardiogram (ECG) is a simple method to diagnose LV hypertrophy and to classify the stage of severity of hypertensive heart disease, but not sensitive compared with echocardiography. Recently, we reported that LVM index (LVMI) was correlated with some ECG variables in untreated patients with essential hypertension. Although the relationship between ECG variables and LVM has been investigated extensively, effects of different antihypertensive drugs on ECG variables and echocardiographic variables have not been determined thoroughly. In particular, changes in ECG and LVM after treatment with a direct vasodilator which would progress LV hypertrophy in patients with hypertension are unclear. We therefore investigated the relationship between ECG voltages and LVM in patients with essential hypertension treated with either angiotensin converting enzyme (ACE) inhibitor which would decrease LVM or direct vasodilator which would increase LVM.

Methods

Patients: Outpatients with essential hypertension were selected from our previous study. All patients underwent routine laboratory studies, including measurements of electrolytes, creatinine, blood urea nitrogen (BUN), and fasting blood glucose level, liver function tests, and urinalysis. The diagnosis of essential hypertension was based on results of laboratory tests and the guidelines of the World Health Organization. Blood pressure was measured using a standard cuff and a sphygmomanometer in the sitting position after a rest of 5 to 10 minutes. Patients were enrolled in the study if their systolic blood pressure (SBP) was > 160 mmHg and/or diastolic blood pressure (DBP) was > 95 mmHg on three separate occasions. Patients with tissue edema or intraventricular conduction block were excluded from the enrollment. In this study, patients were treated with ACE inhibitor (temocapril, n = 11) or direct vasodilator (caldralazine, n = 10). There were 11 men and 10 women with a mean age of 53 ± 13 years (range: 26 to 71 years). Mean body weight, height, and body mass index (BMI) were 62.8 ± 10.6 kg,
159.2 ± 8.9 cm, and 25.6 ± 4.1 kg/m², respectively. No patient had any evidence or history of acute or chronic cardiac, pulmonary, hepatic, or renal disease. Serum creatinine level was below 1.2 mg/dl, and results of urinalysis were normal in all patients.

**Study protocol:** Standard 12-lead ECG and echocardiography were recorded before and after treatment with either temocapril or cadralazine for 12 months. Patients were instructed to eat a normal diet (NaCl 8 to 10 g daily) and to avoid a very high or a low sodium intake. Patients were asked to refrain from caffeine, alcohol, and smoking for 12 hours prior to the examination and to eat a light breakfast about 3 hours before the examination. Conventional transthoracic echocardiography was performed after patients rested for 10 min in the supine position, followed by recording of a standard 12-lead ECG. After a 30 min rest period, blood samples were obtained from the antecubital vein for measurements of plasma renin activity (PRA) and plasma aldosterone concentration (PAC). PRA and PAC were measured by commercial radioimmunoassay kit.

**Echocardiography:** Two-dimensional M-mode echocardiography was performed with a Toshiba SSH-HA phased array ultrasonic sector scanner and a Toshiba FR-06A recorder. Echocardiography was performed with patients in the supine or left lateral decubitus position with the transducer placed in the third to fifth intercostal space at the left sternal border. The tracings used to determine LV dimensions were recorded at or just below the tip of the mitral leaflets. The echocardiograms were read blindly and randomly by two independent observers. The LVM was calculated according to the formula of Devereux and Reichek:

\[
LVM(g) = 1.04 \left[ (LVDd + PWd + IVSd)^3 - LVDd^3 \right] - 13.6.
\]

Where LVDd is the LV internal dimension in diastole, PWd is the LV posterior wall thickness in diastole, and IVSd is the interventricular septal thickness in diastole. The LVMI was determined by dividing the LVM by the patient’s body surface area.

**ECG:** Standard 12-lead ECGs were recorded at a speed of 25 mm/s and at 1 mV/cm according to the recommendations of the American Heart Association. All ECGs were recorded by the same examiner who was unaware of the echocardiographic data. ECG variables were averaged over five consecutive heart cycles. The voltage is expressed in millimeters. The following widely used ECG criteria for detection of LVH were selected in the present study: Sokolow-Lyon voltage (sum of amplitude of S-wave in V₁ and that of R-wave in V₅),[11] Cornell voltage (sum of amplitude of R-wave in aV₅ and that of S-wave in V₃),[12] and sum of R-wave in V₅ and V₆ (RV₅ + RV₆).

**Statistical analysis:** The results are presented as mean ± SD. Inter-group dif-
ferences were analyzed using unpaired t-test. The correlation between LVMI and ECG voltages was analyzed with linear regression analysis. Nonparametric variables were compared with chi-square test. A p value < 0.05 was accepted as statistically significant.

**RESULTS**

Of the 21 patients selected, after a 1 month placebo period, 11 were treated with temocapril (started at 1 mg daily and increased to maximum of 4 mg daily) and 10 were treated with cadralazine (started at 5 mg daily and increased to maximum of 20 mg daily). There were no significant differences in age, sex, duration of hypertension, BMI, systolic and diastolic blood pressures, PRA and PAC between the two groups before antihypertensive treatment. Systolic and diastolic blood pressures were significantly decreased after treatment with temocapril and cadralazine (Table I). However, heart rate was unchanged after the treatment.

**ECG voltages and echocardiographic variables:** ECG and echocardiographic variables did not differ between the 2 study groups before treatment (Tables II

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<td>Number</td>
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<td>Sex (male/female)</td>
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<td>BMI (kg/m²)</td>
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<td>SBP (mmHg)</td>
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<td>Heart rate (bpm)</td>
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<td>PRA (ng/ml/hr)</td>
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<td>PAC (pg/ml)</td>
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BMI = Body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; PRA = Plasma renin activity; PAC = Plasma aldosterone concentration. Mean ± SD. *: p < 0.05, **: p < 0.01 versus before.

<table>
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<th>Table II. Changes in Electrocardiographic Voltages</th>
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<tr>
<td>RV5 (mm)</td>
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<td>RV6 (mm)</td>
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<tr>
<td>RaVL + SV3 (mm)</td>
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<tr>
<td>RV5 + RV6 (mm)</td>
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<td>SV1 + RV5 (mm)</td>
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Mean ± SD.
Table III. Changes in Echocardiographic Variables

<table>
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<tr>
<th></th>
<th>Temocapril before</th>
<th>Temocapril after</th>
<th>Cadralazine before</th>
<th>Cadralazine after</th>
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<tr>
<td>LVMI (g/m²)</td>
<td>123 ± 36</td>
<td>99 ± 33*</td>
<td>102 ± 26</td>
<td>139 ± 36*</td>
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<tr>
<td>LVDd (mm)</td>
<td>46.7 ± 2.9</td>
<td>47.8 ± 3.3</td>
<td>49.5 ± 3.6</td>
<td>51.7 ± 4.1</td>
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<tr>
<td>IVS (mm)</td>
<td>10.4 ± 2.3</td>
<td>8.7 ± 1.3</td>
<td>8.9 ± 2.0</td>
<td>10.1 ± 1.3</td>
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<tr>
<td>PW (mm)</td>
<td>10.2 ± 1.6</td>
<td>8.5 ± 1.2</td>
<td>9.3 ± 1.6</td>
<td>10.7 ± 1.7</td>
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LVMI = left ventricular mass index; LVDd = left ventricular dimension in diastole; IVS = Interventricular septal thickness; PW = left ventricular posterior wall thickness. Mean ± SD, *: p < 0.01 versus before.

Figure. Changes in left ventricular mass index (LVMI, g/m²) and electrocardiographic voltages (mm) after treatment. Change in LVMI was correlated with that in RV₅ + RV₆ (Panel A; p < 0.01) and SV₁ + RV₅ (Panel B; p < 0.01), but not with that in RaVL + SV₃ (Panel C) after treatment with temocapril (●) or cadralazine (○).

and III). After the treatment, both Sokolow-Lyon voltage and RV₅ + RV₆ tended to decrease in the temocapril group (NS), but to increase in the cadralazine group (NS). LVMI determined by echocardiography was decreased in the temocapril group (p < 0.01), but increased in the cadralazine group (p < 0.01). After the treatment, IVS and PW tended to decrease in the temocapril group and to increase in the cadralazine group.

Relation of electrocardiographic voltages to LVMI after the treatment: As a whole group, the change in LVMI was significantly correlated with that in RV₅ + RV₆ and Sokolow-Lyon voltage (r = 0.73, p < 0.01 and r = 0.70, p < 0.01, respectively), but not with that of RaVL + SV₃ after treatment with temocapril or
cadralazine (Figure). This was also true for the temocapril group; that is, the change in LVMI was significantly correlated with that in \( RV_3 + RV_6 \) and \( SV_1 + RV_3 \) \((r = 0.67, \ p < 0.05\) and \( r = 0.63, \ p < 0.05\), respectively), but not with that in \( RaV_L + SV_3 \) \((r = 0.49, \ NS)\). However, in the cadralazine group, the change in LVMI was not correlated with that in \( RV_3 + RV_6 \), \( SV_1 + RV_3 \) and \( RaV_L + SV_3 \) \((r = 0.49, \ r = 0.53, \) and \( r = -0.19, \) respectively, \( NS\)). These results suggest that ECG criteria are not so sensitive to detect the progression of LVM as to detect the regression of LVM.

**DISCUSSION**

**Major findings of the present study:** Major findings of the present study are as follows. First, diverse effects on LVMI, that is, a decrease in LVMI after temocapril and an increase in LVMI after cadralazine, were observed after treatment of essential hypertension. Secondly, after treatment of essential hypertension with temocapril or cadralazine, the change in LVMI as a whole was correlated positively with that in Sokolow-Lyon voltage and \( RV_3 + RV_6 \), but not with that in Cornell voltage. Thus, some ECG variables are useful to detect the changes in LVMI after treatment when echocardiographic LVMI was regarded as a gold standard for anatomical LVM. To our knowledge, this is the first report to indicate diverse effects of antihypertensive drugs on LVMI were correlated with ECG voltages in patients with essential hypertension.

**Factors affecting ECG voltage:** ECG voltage can be affected by changes in LVM, that is, the number\(^{13} \) or size of fibers\(^{14} \) in the hypertrophied ventricle. ECG voltage is significantly correlated with the LVM estimated by angiography\(^ {15,16} \) and echocardiography.\(^ {5,17} \) An increased ECG voltage is also related to the ventricular surface, and the intracavitary blood volume, the distance from the ventricular surface to the chest wall.\(^ {18} \) Feldman et al.\(^ {19} \) have reported that left lateral chest leads clearly reflect changes in LV size, especially in relation to the distance between the LV surface and electrodes on the chest wall. Acute changes in LV dimension were positively correlated with those in R wave voltages in the left lateral chest leads in patients without myocardial infarction.\(^ {20} \)

In the present study, changes in ECG variables were correlated with those in echocardiographic LVM with each patient served as the internal control. Therefore, it is less likely that an extracardiac factor would affect ECG voltages. Cadralazine could lead to fluid retention.\(^ {21} \) If so, ECG voltages would have rather decreased.

**Change of ECG characteristics after treatment:** ECG voltages were useful to detect LV hypertrophy in untreated patients with hypertension\(^ {6} \) or in a large
However, it is unclear which ECG criterion is suitable to reflect regression or progression of LV hypertrophy after long-term antihypertensive treatment in patients with essential hypertension. Some investigators reported that hypertrophy regression after treatment was associated with lowering of blood pressure and with disappearance of high ECG voltage in about half of cases. However, antihypertensive drugs used were not specified in their study. It is clearly shown that some classes of antihypertensive drugs regress LV hypertrophy, but others do not. Sen reported that direct vasodilators such as hydralazine or minoxidil increased LV hypertrophy despite a reduction of blood pressure. In contrast, a line of evidence for favorable effects of ACE inhibitors on LV hypertrophy in hypertensive patients was demonstrated. This salutary effect could be attributed not only to the reduction in afterload but to local and/or systemic effects on angiotensin II formation. Accordingly, temocapril would decrease LVM while cadralazine would lead to the opposite change as reported previously. Our working hypothesis was that diverse change in LVM would be reflected in changes in some selected ECG voltages. This was actually observed in the present study.

However changes in ECG voltage during antihypertensive treatment may not be sensitive compared with that seen in untreated hypertension, because it is not certain that abnormality can regress after relief of the afterload, once there has been LV hypertrophy with possible fibrosis. In the present study, ECG criteria were not so sensitive to detect the progression of LVM (cadralazine group) as to detect the regression of LVM (temocapril group). It is well known that interstitial myocardial collagen could attenuate high QRS voltage in hypertension. It is therefore plausible that accumulation or removal of interstitial myocardial collagen during antihypertensive treatment may affect the disassociation between ECG variables and LVM in this study.

Methodological consideration: There were many unresolved issues concerning ECG voltages. Change in QRS voltage does not correlate with that in LVM precisely, because QRS voltage results from the complex electrical activity of the entire heart. Cardiac factors such as electrical activity, structure character and myocardial histological character could influence QRS voltage. Hypertrophy of the ventricle involves cardiac muscle cells, fibroblasts and collagen. Extracardiac factors such as body fluid, lung effect, tissue edema and distance between the heart and the chest wall could also influence QRS voltage recorded from the body surface. Occasionally, obesity masks the detection of LV hypertrophy. However, body weight and BMI were unchanged throughout the treatment period in this study.

Devereux et al. observed a correlation between measurements of LVM determined by echocardiography and at necropsy. However, Missourris et al.
reported that there was a discrepancy between LVM measurements obtained by echocardiography and those obtained by magnetic resonance imaging in hypertensive patients, especially in patients with more severe hypertrophy. Thus, the LVM may be overestimated by echocardiography, although patients with severe hypertrophy were not included in the present study. In the present study, number of patients for each treatment limb was small, and this could hamper our result especially in the cadrallazine group. It is not desirable that monotherapy with cadrallazine would be used because of progression of LVMI as shown in the present study. Further studies are needed to determine the correlation between electrocardiographic variables and LVM in patients with hypertension after treatment with other classes of antihypertensive drugs.

Although limited for these reasons, the present study showed changes in voltage criteria of RV5 + RV6 and Sokolow-Lyon were useful to assess the change in LVM after antihypertensive treatment in patients with essential hypertension.

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REFERENCES