Indices of left ventricular voltage on electrocardiogram are closely associated with serum cardiac troponin I levels in normotensive Japanese individuals

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Abstract
The high-sensitivity cardiac troponin I (hs-cTnI) in serum can increase due to an increase in left ventricular (LV) overload in individuals with hypertension. Since LV voltage on an electrocardiogram (ECG) reflects LV load, it is possible that LV voltage is closely associated with hs-cTnI in individuals without hypertension. This study investigated the association between LV voltage indices and serum hs-cTnI levels in normotensive Japanese individuals.

Subjects who visited the Enshu Hospital for a health check-up were screened for their eligibility. Subjects with renal dysfunction, cancer, active inflammatory disease, or a history of cardiovascular events were excluded, as were subjects with obvious ST segment or T wave abnormality, Wolff–Parkinson–White syndrome, pacemaker implantation, or frequent arrhythmia in the ECG. Exclusion of individuals with hypertension left 803 subjects (54.8±11.3 years) for final inclusion. The R wave voltage in lead V5 (RV5 voltage), the Sokolow–Lyon voltage (a sum of the QRS wave (a complex wave consists of Q, R, and S wave) of the S wave voltage in lead V1 and the R wave voltage in lead V5), and the Cornell product (a product of QRS duration and QRS voltage) were evaluated by ECG as LV voltage indices. Laboratory measurements included serum hs-cTnI levels. Possible associations between indices of LV voltage on ECG and serum hs-cTnI levels were cross-sectionally investigated in the normotensive subjects.

The median values [interquartile range] of hs-cTnI and BNP were 2.1 [1.4–3.0] and 13.8 [7.7–24.9] pg/mL, respectively. Multivariate regression analysis identified that the levels of hs-cTnI, but not BNP, were significantly associated with RV5 voltage (β 0.090, P = 0.0087), Sokolow–Lyon voltage (β 0.112, P = 0.0009), and Cornell product (β 0.101, P = 0.009) after adjustment for possible confounding factors. Moreover, the RV5 voltage, Sokolow–Lyon voltage, and Cornell product were significantly associated with the hs-cTnI levels after adjustment for possible confounding factors including ECG findings (β 0.100, P = 0.0075; β 0.125, P = 0.0010; and β 0.096, P = 0.0116, respectively).

Indices of LV voltage in ECG had close associations with serum hs-cTnI levels in normotensive subjects. These findings support that the ECG findings of LV voltage have significant associations with slight myocardial micro-damage even in normotensive subjects.

Abbreviations: BNP = B-type natriuretic peptide, BP = blood pressure, ECG = electrocardiogram, hs-cTnI = high-sensitivity cardiac troponin I, LV = left ventricular, LVH = left ventricular hypertrophy.

Keywords: B-type natriuretic peptide, cardiac troponin I, electrocardiogram, left ventricular voltage, myocardial micro-damage
1. Introduction

Elevated serum myocardial constitutive proteins, such as cardiac troponins T and I, is a clinically important finding in acute coronary syndrome,[1,2] and recently developed assays for these proteins are enabling better immediate diagnosis through improved detection of myocardial injury.[3,4] These high-sensitive assays can detect very low levels of cardiac troponins, and therefore, cardiac troponin levels are often found to be slightly elevated or varied around the reference ranges in individuals without acute coronary syndrome. Such alterations in cardiac troponin levels are mainly associated with nonischemic myocardial micro-injury due to asymptomatic cardiac overload.[5,6]

Hypertension is an established risk factor for cardiovascular disease that commonly causes cardiac overload and increased cardiac troponin levels.[7,8] Individuals with hypertension experience increased arterial pressure and vascular resistance that yields left ventricular (LV) load and potentially, left ventricular hypertrophy (LVH) that is usually identified by electrocardiogram (ECG). On the other hand, findings of LVH based on ECG predict future development of hypertension in normotensive general population.[9] This means that the LV load might increase even in subjects without hypertension. Moreover, we recently demonstrated that ECG findings relevant to the QRS wave (a complex waveform consists of Q, R, and S wave) are associated with serum levels of high-sensitivity cardiac troponin (hs-cTnI) in the general population including subjects with hypertension.[10] These findings imply that modest increases in LV load can follow slight increases in arterial pressure and the subsequent myocardial micro-injury can be detected as an increase in cardiac troponin I level that is reflected in ECG findings relevant to the QRS wave. Nevertheless, the relationship between ECG findings and serum cardiac troponin I levels in subjects without hypertension remains unclear. The present study thus investigated possible associations between indices of LV voltage on ECG, which are mainly assessed by QRS voltage in a single lead or combination of findings of 12 leads ECG, and serum hs-cTnI levels in normotensive individuals without obvious ischemic heart disease.

2. Methods

The present study enrolled normotensive individuals who were undergoing their annual health check-up. Possible associations between indices of LV voltage on ECG and serum hs-cTnI levels were cross-sectionally investigated in the normotensive subjects. The study protocol was approved by the ethics committees of Enshu Hospital, and was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from each subject and all data used in the study were anonymized.

2.1. Subjects

Subjects who visited Enshu Hospital in 2015 for a health check-up (n=4200) were screened for their eligibility to participate in the present study. Subjects with renal dysfunction (creatinine ≥1.5 mg/dL), cancer, active inflammatory disease, or a history of cardiovascular events (stroke, myocardial infarction, and heart failure) were excluded, as were subjects with obvious ST segment or T wave abnormality, Wolff–Parkinson–White syndrome, pacemaker implantation, or frequent arrhythmia (including atrial fibrillation and atrial flutter) in the standard 12-lead ECG. Exclusion of individuals with hypertension left 803 subjects for final inclusion in this study (Supplementary Fig. 1, http://links.lww.com/MD/E176).

For all subjects, blood samples were taken early in the morning after an overnight fast for laboratory measurements. Blood pressure (BP) was also measured in the nondominant arm using a validated oscillometric technique (HEM-7070; Omron Corporation, Kyoto, Japan) in subjects in a seated position. Three consecutive BP measurements were taken at 2-minute intervals, and the mean of the second and third measurements was recorded as the BP. Subjects taking antihypertensive medications or with systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg were defined as having hypertension.[11] Subjects taking lipid-lowering medications or with high-density lipoprotein cholesterol <40 mg/dL, low-density lipoprotein cholesterol ≥140 mg/dL, or triglycerides ≥150 mg/dL were defined as having dyslipidemia.[12] Subjects taking blood glucose-lowering medication or with fasting plasma glucose levels ≥126 mg/dL were defined as having diabetes.[13] Since cigarette smoking is one of the major risk factors for ischemic cardiovascular disease, smoking status was asked in each subject.

2.2. Biochemical analysis

Biochemical tests were performed using standard laboratory assays. Plasma B-type natriuretic peptide (BNP) levels were determined using a commercially available chemiluminescence enzyme immunoassay (MI02 Shionogi BNP kit; Shionogi, Osaka, Japan). Serum levels of hs-cTnI were measured by the ARCHITECT high-sensitive Troponin I assay according to the manufacturer’s instructions (Abbott, Tokyo, Japan).

2.3. Assessment of LV voltage in ECG recordings

A resting 12-lead ECG was recorded in all subjects in the supine position using a portable filing system (Cardiostar FCP-7431; Fukuda Denshi, Tokyo, Japan), and analyzed automatically by a standard 12-lead ECG analysis. ECG findings relevant to the LV voltage were assessed by the R wave voltage in lead V5 and the Sokolow–Lyon voltage, a sum of the QRS voltage of the S wave in lead V1 and the R wave in lead V5.[14–22] The Cornell product, based on the QRS duration and QRS voltage [a sum of the S wave in lead V3 and the R wave in lead aVL] was also evaluated.[17–22] Simultaneously, ECG features relevant to the QRS wave were investigated by measuring the PQ interval (duration from the onset of the P wave to the onset of the QRS wave), QRS voltage, QRS duration, corrected QT (QTc) interval, and QRS axis. In Fukuda Denshi ECG system, the automatic measurements of PQ interval, QRS duration, and QT interval are performed in all leads and each value is expressed as the average of them. QT interval is defined as the duration from QRS initiation to the end of T wave, and then heart rate corrected QT interval, QTc interval, is calculated using Bazett’ formula.[23]

2.4. Statistical analysis

Data were analyzed using IBM SPSS Statistics 19 (IBM Corp., Chicago, IL). Dichotomous variables (sex, smoking status, and medications) were assigned values of 0 (female, nonsmoker, and no) or 1 (male, smoker, and yes). Data with a normal distribution are expressed as the mean ± standard deviation. Data that were not normally distributed (BNP and hs-cTnI) are expressed as the median with interquartile range and were evaluated in
multivariate and logistic regression analyses after log transformation. Comparative analyses of continuous variables were performed using t tests. Two-tailed P-values < .05 were considered significant.

3. Results

Table 1 presents the subject characteristics. The median values of hs-cTnI and BNP were 2.1 and 13.8 pg/mL, respectively. The number (%) of subjects complicated with dyslipidemia, diabetes mellitus, and obesity (body mass index ≥25 kg/m²) was 384 (43.3%), 33 (4.1%), and 105 (13.1%), respectively. When subjects were divided into quartiles according to the hs-cTnI value, each ECG finding regarding LV voltage (RV5 voltage, Sokolow-Lyon voltage, and Cornell product) showed a significant trend for an increase across the quartiles (Table 1).

Results of univariate regression analysis of factors possibly correlated with the levels of hs-cTnI are shown in Supplementary Table 1, http://links.lww.com/MDE/177. Then, multivariate analysis was conducted taking factors significantly correlated with the hs-cTnI level in univariate analyses as well as conventional cardiovascular risk factors such as smoking status, BP, lipid profiles, and glucose metabolism as independent variables. By the multivariate regression analysis, hs-cTnI levels were significantly associated with all of the measured LV voltage indices after adjustment for age, gender, body mass index, and smoking status (Table 2, Model 1). These associations remained significant after additional adjustment for BP, heart rate,
4. Discussion

The main findings of the present study are that:
hs-cTnI levels, but not BNP levels, were significantly associated with R5 voltage, Sokolow–Lyon voltage, and Cornell product; only the LV voltage indices were significantly associated with the hs-cTnI levels by multivariate regression analysis among the evaluated ECG features in normotensive subjects.

These results indicate that the ECG finding of LV voltage was significantly associated with slight myocardial micro-damage even in normotensive subjects without obvious ischemic heart disease.

LV load has been conventionally evaluated using the ECG indices obtained from a single lead, such as the R wave in lead V5, or from a combination of ECG findings relevant to the QRS wave, such as the Sokolow–Lyon voltage and Cornell product.17–22 Also, because an increased LV voltage reflects augmented arterial pressure load in subjects with hypertension, LVH findings are thought to indicate damage to one of the main target organs of arterial hypertension.9–14 However, BP shows short-term and long-term variability, producing fluctuations, even in individuals not clinically diagnosed as hypertensive,24 and an increased LV voltage might reflect an increase in LV load due to a transient and/or unidentified BP elevation. In cases of masked hypertension, such unidentified and abnormal BP elevation is recorded at out of office, while white-coat hypertension refers to transient BP elevation only in the medical setting.14 Thus, LV voltage indices are useful for managing both

Table 2
Multivariate regression analyses between high-sensitivity cardiac troponin I levels and indices of left ventricular voltage in the electrocardiogram of normotensive subjects (n = 803).

| Variable | Analysis 1: Left ventricular voltage using the R wave voltage in V5 | Analysis 2: Left ventricular voltage using the Sokolow–Lyon voltage | Analysis 3: Left ventricular voltage using the Cornell product |
|----------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| β        | P-value                                                      | β                                                             | P-value                                                      |
| hs-cTnI (pg/mL), Model 1 | 0.126 <.001 | 0.147 <.001 | 0.095 <.05 |
| hs-cTnI (pg/mL), Model 2 | 0.094 .05 | 0.115 <.01 | 0.083 <.05 |
| hs-cTnI (pg/mL), Model 3 | 0.100 <.01 | 0.125 <.001 | 0.093 <.05 |
| hs-cTnI (pg/mL), Model 4 | 0.109 <.01 | 0.125 <.01 | 0.096 <.05 |

Model 1 was adjusted for age (yr), male gender (yes or no), smoking status (yes or no), and body mass index (kg/m²).
Model 2 was adjusted for heart rate (bpm), systolic blood pressure (mm Hg), creatinine (mg/dL), fasting plasma glucose (mg/dL), high-density lipoprotein cholesterol (mg/dL), low-density lipoprotein cholesterol (mg/dL), and triglyceride (mg/dL) in addition to the factors included in Model 1.
Model 3 was adjusted for B-type natriuretic peptide (pg/ml) in addition to the factors included in Model 2.
Model 4 was adjusted for possible medications in addition to the factors included in Model 3.
hs-cTnI = high-sensitivity cardiac troponin I.

Table 3
Multivariate regression analyses between indices of left ventricular voltage in the electrocardiogram and B-type natriuretic peptide levels in normotensive subjects (n = 803).

| Variable | Analysis 1: Left ventricular voltage using the R wave voltage in V5 | Analysis 2: Left ventricular voltage using the Sokolow–Lyon voltage | Analysis 3: Left ventricular voltage using the Cornell product |
|----------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| β        | P-value                                                      | β                                                             | P-value                                                      |
| BNP (pg/mL), unadjusted | −0.038 .278 | −0.071 <.05 | 0.082 <.05 |
| BNP (pg/mL), Model 1 | 0.001 .975 | −0.034 .463 | −0.039 .237 |
| BNP (pg/mL), Model 2 | −0.028 .392 | −0.049 .139 | −0.049 .130 |
| BNP (pg/mL), Model 3 | −0.030 .363 | −0.051 .114 | −0.045 .164 |

Model 1 was adjusted for age (yr), male gender (yes or no), smoking status (yes or no), and body mass index (kg/m²).
Model 2 was adjusted for heart rate (bpm), systolic blood pressure (mm Hg), creatinine (mg/dL), fasting plasma glucose (mg/dL), high-density lipoprotein cholesterol (mg/dL), low-density lipoprotein cholesterol (mg/dL), and triglyceride (mg/dL) in addition to the factors included in Model 1.
Model 3 was adjusted for possible medications in addition to the factors included in Model 2.
BNP = B-type natriuretic peptide.
The clinical significance of highly sensitive cardiac troponin assays that can detect very low levels is not only the immediate diagnosis of acute coronary syndrome, but also the detection of myocardial micro-damage.\[1,2\] Several studies demonstrated the usefulness of cardiac troponin for predicting new onset hypertension, heart failure, and cardiovascular events, in addition to coronary heart disease.\[6,29,30\] In addition, we previously revealed that hs-cTnI levels were significantly associated with ECG findings relevant to the QRS waves in the general population.\[13\] Thus, since cardiac troponin I is reportedly superior to troponin T for detecting electrocardiographic cardiac injury, we decided to evaluate hs-cTnI in subjects with hypertension and normotensive subjects without a diagnosis of hypertension. Although R voltage in V5 lead had traditionally been used for the assessment of LVH, the R wave index by Sokolow–Lyon voltage and Cornell product was developed for indices of LVH.\[17\] The clinical significance of high-sensitivity cardiac troponin I (hs-cTnI) levels in the general population was demonstrated in our previous study.\[31\] Herein, we revealed a close association between LV voltage indices and hs-cTnI level, even in normotensive individuals.

### Table 4
Multivariate regression analyses demonstrating findings of electrocardiogram possibly associated with high-sensitivity cardiac troponin I levels in normotensive subjects (n=803).

| Variable | Analysis 1: Left ventricular voltage using the R wave voltage in V5 | Analysis 2: Left ventricular voltage using the Sokolow–Lyon voltage | Analysis 3: Left ventricular voltage using the Cornell product |
|----------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
|          | β      | P-value | β      | P-value | β      | P-value |
| Model 1  |        |         |        |         |        |         |
| R wave voltage in V5, mV | 0.11  | <.01  | –      | –      | –      | –      |
| Sokolow–Lyon voltage, mV | –      | –      | 0.124  | <.001  | –      | –      |
| Cornell product, mm-ms | –      | –      | 0.027  | .40    | 0.021  | .53    |
| PQ interval, ms | 0.018  | .61   | 0.027  | .50    | –      | –      |
| GRS duration, ms | 0.019  | .61   | 0.027  | .50    | –      | –      |
| Corrected QT interval, ms | –0.025 | .51   | –0.023 | .49    | –0.019 | .57    |
| GRS axis, ° | 0.027  | .46   | 0.023  | .23    | 0.061  | .08    |
| Model 2  |        |         |        |         |        |         |
| R wave voltage in V5, mV | 0.091  | <.05   | –      | –      | –      | –      |
| Sokolow–Lyon voltage, mV | –      | –      | 0.10   | <.01   | –      | –      |
| Cornell product, mm-ms | –      | –      | 0.024  | .46    | 0.017  | .60    |
| PQ interval, ms | 0.017  | .64   | 0.024  | .46    | 0.017  | .60    |
| GRS duration, ms | –0.001 | .98   | 0.018  | .61    | –      | –      |
| Corrected QT interval, ms | 0.003  | .94   | 0.007  | .85    | 0.007  | .84    |
| GRS axis, ° | 0.028  | .44   | 0.023  | .48    | 0.055  | .11    |
| Model 3  |        |         |        |         |        |         |
| R wave voltage in V5, mV | 0.097  | <.05   | –      | –      | –      | –      |
| Sokolow–Lyon voltage, mV | –      | –      | 0.11   | <.01   | –      | –      |
| Cornell product, mm-ms | –      | –      | 0.022  | .50    | 0.015  | .65    |
| PQ interval, ms | 0.016  | .66   | 0.022  | .50    | 0.015  | .65    |
| GRS duration, ms | 0.012  | .76   | 0.031  | .51    | –      | –      |
| Corrected QT interval, ms | –0.025 | .56   | –0.017 | .66    | –0.012 | .73    |
| GRS axis, ° | 0.026  | .48   | 0.022  | .37    | 0.057  | .09    |
| Model 4  |        |         |        |         |        |         |
| R wave voltage in V5, mV | 0.099  | <.01   | –      | –      | –      | –      |
| Sokolow–Lyon voltage, mV | –      | –      | 0.12   | <.001  | –      | –      |
| Cornell product, mm-ms | –      | –      | 0.010  | .78    | 0.003  | .99    |
| PQ interval, ms | 0.015  | .69   | 0.010  | .78    | 0.003  | .99    |
| GRS duration, ms | –0.015 | .85   | 0.016  | .68    | –      | –      |
| Corrected QT interval, ms | –0.029 | .49   | –0.031 | .46    | –0.032 | .42    |
| GRS axis, ° | 0.030  | .42   | 0.030  | .40    | 0.069  | .06    |

Model 1 was adjusted for age (yr), male gender (yes or no), smoking status (yes or no), and body mass index (kg/m²).
Model 2 was adjusted for heart rate (bpm), systolic blood pressure (mm Hg), creatinine (mg/dL), fasting plasma glucose (mg/dL), high-density lipoprotein cholesterol (mg/dL), low-density lipoprotein cholesterol (mg/dL), triglyceride (mg/dL) in addition to the factors included in Model 1.
Model 3 was adjusted for B-type natriuretic peptide (pg/mL) in addition to the factors included in Model 2.
Model 4 was adjusted for possible medications in addition to the factors included in Model 3.
T, even within the normal range, could predict future cardiovascular disease in an additive and complementary way. Interestingly, their report also revealed that the predictive power with respect to cardiovascular events was different between troponin I and troponin T.\textsuperscript{[25]} Thus, although the mechanism underlying those differences was not clear, the findings indicate that the combination of both troponins might be useful as biomarkers.

Recently, Bang et al reported that electrocardiographic LVH findings predict cardiovascular morbidity and mortality in large hypertensive samples\textsuperscript{[30]} and thus the presence of LVH findings and its reduction have shown previously\textsuperscript{[17,18]} In addition, we revealed the usefulness of LVH voltage for the detection of future hypertension in the general population.\textsuperscript{[12]} However, the clinical significance of the LV voltage in normotensive individuals was not evaluated sufficiently. Hence, to investigate the clinical meaning of LV voltage in normotensive individuals, we analyzed the association between LV voltage indices and levels of hs-cTnI in the present study. Findings obtained from the present study revealed that ECG findings of LV voltage indicate myocardial micro-damage, which may reflect masked hypertension, and provide important information even in individuals who had not diagnosed as hypertension.\textsuperscript{[14,34,35]} Accordingly, measurement and assessment of LV voltage in ECG are easy in various clinical situations and may be useful for discriminating individuals at increased cardiovascular risk among apparently healthy individuals.

BNP is a neurohormonal factor released mainly from the left ventricle and an established biomarker of heart failure reflecting LV pressure load and volume load that is therefore frequently used as an indicator for heart failure.\textsuperscript{[19–30]} Additionally, we previously reported that BNP levels predict new-onset hypertension, atrial fibrillation, and recurrence of angina pectoris.\textsuperscript{[39–41]} In the present study, BNP levels were significantly associated with hs-cTnI levels, but not with the LV voltage indices. Although the underlying mechanisms for this discrepancy are not clear, we speculate that the BNP levels were nearly within normal reference range and thus failed to reflect slight increases in arterial pressure load, while the hs-Ctln levels could detect faint constitutive changes reflecting increased LV load. Alternatively, the present results could be attributable to biological differences in kinetics and clearance of BNP and TnI, whereby BNP potentially failed to reflect transient and latent pressure load due to its very short half-life. Thus, assessment of hs-cTnI levels might be useful to detect latent or minor cardiac changes in individuals without hypertension.

5. Limitations

The present study has several limitations, and thus the findings obtained should be interpreted with caution. First, this was a cross-sectional study and the subject backgrounds were heterogeneous. Second, the causative relationship between hs-cTnI levels and LV voltage in ECG was not investigated, and a longitudinal follow up study of hs-cTnI levels and LV voltage in ECG or biological assessments are needed to ascertain the underlying mechanisms of close association between LV voltage and hs-cTnI levels. Third, the enrolled subjects were mainly middle-to-old ages. Hence, the obtained results may not apply to younger subjects who might indicate false-positive findings in LVH. Fourth, ischemic heart disease was not been completely excluded in our subjects because they did not undergo an exercise stress test or coronary angiography. Further investigations with a larger population and a longitudinal design are also necessary for definite conclusions to be drawn.

6. Future directions

ECG findings of LV voltage reflect myocardial micro-damage and provide important information even in individuals with normal BP. Measurement and assessment of LV voltage in ECG are easy in various clinical situations and may be useful for discriminating individuals at increased cardiovascular risk among apparently healthy individuals.

7. Conclusions

Indices of LV voltage including the Sokolow–Lyond voltage and Cornell product are closely associated with serum hs-cTnI levels in normotensive individuals. These findings support that the ECG findings of LV voltage have significant associations with slight myocardial micro-damage in normotensive subjects.

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