



# Addition of N-terminal Pro-B-type Natriuretic Peptide Levels to Electrocardiography Criteria for Detection of Left Ventricular Hypertrophy: The ARIRANG Study

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Received: 28 April 2014  
Accepted: 3 December 2014

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Funding: This work was supported by a research grant from Yonsei University Wonju College of Medicine (YUWCM 2013-26).

The utility of electrocardiography (ECG) in screening for left ventricular hypertrophy (LVH) in general populations is limited mainly because its low sensitivity. B-type natriuretic peptide (BNP) is released due to the remodeling processes of LVH and could improve the diagnostic accuracy for the ECG criteria for LVH. We hypothesized that addition of BNP levels to ECG criteria could aid LVH detection compared with ECG alone in a general population. We enrolled consecutive 343 subjects from a community-based cohort. LVH was defined as LV mass index  $> 95 \text{ g/m}^2$  for females and  $> 115 \text{ g/m}^2$  for males according to echocardiography. The area under the receiver operator characteristic (ROC) curve to detect LVH was 0.55 (95% confidence interval [CI], 0.50-0.61) in Sokolow-Lyon criteria and 0.53 (0.47-0.59) in the Cornell voltage criteria. After addition of N-terminal-proBNP levels to the model, the corresponding areas under the ROC were 0.63 (0.58-0.69) and 0.64 (0.59-0.69), respectively. *P* values for the comparison in areas under the ROC for models with and without N-terminal-proBNP levels were  $< 0.001$ . These data suggest that addition of N-terminal-proBNP levels to ECG criteria could significantly improve the diagnostic accuracy of LVH in general populations.

**Keywords:** Hypertrophy; Left Ventricular; Electrocardiography; Natriuretic Peptides

## INTRODUCTION

Left ventricular hypertrophy (LVH) is an important risk factor in hypertensive patients and the general population. LVH can lead to a 5-10-fold increase in cardiovascular risk, which is similar to the increase seen in patients with a history of myocardial infarction (1-4). LVH has important implications for assessment of the future risk of cardiovascular disease and for decision-making regarding interventions other than antihypertensive treatment, such as lipid-lowering treatment and lifestyle modifications (5). Therefore, accurate and early diagnosis of LVH is an important component of the care of patients who have hypertension and for those who do not have hypertension.

Echocardiography permits reliable, non-invasive estimation of left ventricular mass. It has proved to be a sensitive and practical tool for the detection of LVH (6). However, echocardiography is not affordable for community-wide screening for LVH because it is expensive, and measurements of LV mass are time-consuming. Hence, simple tools are needed to facilitate the identification and screening of LVH in hypertensive patients and the general population.

Until recently, electrocardiography (ECG) was a simple and

acceptable tool for screening LVH in the general population. More than 30 ECG indices for the diagnosis of LVH based on standard 12-lead ECG have been described. However, the diagnostic values of various indices are modest because they have high specificity but very low sensitivity. Furthermore, the accuracy of ECG criteria for the detection of LVH was evaluated in Western countries. The diagnostic value of these indices in Asian populations is not clear because of physiological and genetic differences.

Natriuretic peptide acts a counter-regulatory hormone in a compensatory response to pressure and volume overload in LVH (7). N-terminal pro-B-type natriuretic peptide (NT-proBNP) has been positively associated with, LV strain, activation of the renin-angiotensin-aldosterone system, myocardial fibrosis and myocyte necrosis (8, 9). In addition, recent evidence suggests that NT-proBNP could have a role in the diagnosis of LVH (10, 11). Whether measurement of NT-proBNP levels can be an additional tool for LVH screening in the general population is not known.

Here, we compared the diagnostic accuracy of ECG criteria alone with a combination of measurements of ECG and of NT-proBNP levels for the detection of LVH in a rural population in

Korea. We hypothesized that the latter could improve the detection of LVH compared with ECG alone.

## MATERIALS AND METHODS

### Study population

The Korean Genome and Epidemiology Study on Atherosclerosis Risk of Rural Areas in the Korean General Population (KoGES-ARIRANG) is a population-based prospective cohort study to assess the prevalence, incidence and risk factors for chronic degenerative disorders such as hypertension, diabetes mellitus (DM), osteoporosis, and cardiovascular disease (12-16). We used ancillary data from KoGES-ARIRANG. KoGES-ARIRANG invited all adults aged 40-70 yr who resided in the rural areas of Wonju and Pyengchang in Korea to participate in the study (12-16).

In the present study, we investigated 343 adults from the KoGES-ARIRANG cohort ( $n = 1,954$ ) who had previously undergone ECG, echocardiography, and measurement of NT-proBNP levels. For the present study, all participants underwent a complete cardiovascular evaluation following 8 hr of fasting at first visit day, which included: 1) history, physical examination, and anthropometric analysis; 2) measurement of heart rate and blood pressure (BP, measured after 10 min resting in a sitting position, was expressed as the average of three consecutive measurements taken from each arm); 3) measurement of fasting serum glucose and insulin levels (in subjects not receiving insulin and/or oral hypoglycemic agents); 4) measurement of fasting plasma lipids (i.e., concentrations of triglyceride, high-density lipoprotein cholesterol [HDL-C], total cholesterol, and low-density lipoprotein cholesterol [LDL-C]); 5) measurement of NT-proBNP; and 6) echocardiography and electrocardiography (12-16). Past medical histories of subjects such as hypertension, diabetes mellitus and dyslipidemia were based on history taking. Subjects with systolic dysfunction (ejection fraction  $\leq 55\%$ ,  $n = 127$ ) or renal dysfunction (estimated glomerular filtration rate  $< 60$  mL/min/ $1.73$  m<sup>2</sup>,  $n = 154$ ) were excluded from the analysis (17).

### Echocardiography

Echocardiography was undertaken by 3 cardiologists in harmonic imaging mode by use of a 3-MHz transducer and commercial ultrasound system (Vivid-7; General Electric-Vingmed, Milwaukee, WI, USA). All echocardiographic data were analyzed offline using a dedicated automated software (EchoPAC PC, Version 112; GE Health Care, Milwaukee, WI).

The internal dimensions, wall thickness, and ejection fraction of the left ventricle (i.e., LVEF, by the modified Simpson's rule) were measured according to recommendations (18). LV mass was calculated as recommended by the American Society of Echocardiography using the equation: LV mass =  $1.04 \times ([PW + VS + LVDD]^3 - [LVDd]^3) \times 0.8 + 0.6$  where PW is the M-mode thickness of the posterior wall of the LV, VS is the M-mode thickness

of the interventricular septum, and LVDD is the M-mode LV dimension in the short-axis view at end-diastole (12, 19). To correct for body surface area, the LV mass index (LVMI) was calculated as LV mass/body surface area. Body surface area (BSA) was calculated using the formula:  $BSA = 0.007184 \times \text{weight}^{0.425} \times \text{height}^{0.725}$  (m<sup>2</sup>). LVH was defined as LVMI  $> 95$  g/m<sup>2</sup> for females and  $> 115$  g/m<sup>2</sup> for males (17). Relative wall thickness (RWT), which increases with concentric remodeling and concentric hypertrophy, was calculated as  $2 \times PW/LVDD$ . Three left atrial (LA) dimensions were used to calculate LA volume as an ellipse using the formula: LA volume =  $\pi/6$  (SA1  $\cdot$  SA2  $\cdot$  LA) where SA1 = M-mode LA dimension, and SA2 and LA are measurements of the short- and long-axis with the apical four-chamber view at ventricular end-systole, respectively (17). The LA volume index was calculated by dividing the LA volume by the BSA (m<sup>2</sup>). Transmitral inflow velocities were measured using pulsed-wave Doppler (PWD) ultrasound and the apical four-chamber view, with the sample volume placed at the tips of mitral-valve leaflets. Measurements of transmitral early diastolic (E-wave) and atrial (A-wave) velocities were taken to calculate the E/A ratio and E-wave deceleration time. Tissue Doppler imaging (TDI) and the apical four-chamber view were used to measure LV myocardial velocities, with the sample volume placed at the septal mitral annulus (12, 20, 21). Measurements comprised the early diastolic velocity (E') and late diastolic velocity (A'). The E/E' ratio was then calculated (12, 22).

### ECG

A standard, at rest, 12-lead recording was made during quiet respiration, with subjects in the supine position. The electrocardiogram was recorded at 25 mm/s and 0.1 mV/mm standardization. ECG criteria for the diagnosis of LVH were the Sokolow-Lyon criteria (S in V1+R in V5 or V6 [whichever was larger]  $> 35$  mm) and the Cornell voltage criteria (S in V3+R in aVL  $> 28$  mm in males, and S in V3+R in aVL  $> 20$  mm in females) (23, 24).

### Measurement of plasma levels of NT-proBNP

Blood samples were obtained from fasting participants in the morning. Subjects were in the supine position, and blood obtained from the antecubital vein. Samples were transferred immediately to pre-chilled tubes containing ethylenediamine tetra-acetic acid and then stored at  $-70^\circ\text{C}$  for future analyses (25). Plasma levels of NT-proBNP were measured using an electrochemiluminescence assay (Elecsys 2010<sup>®</sup>; Roche Diagnostics, Indianapolis, IN, USA) using established methods (26). The lower limit of detection was 4 pg/mL. The mean coefficient variation for these samples was 2.7%.

### Statistical analyses

Statistical analyses were carried out using SPSS v20 (SPSS, Chicago, IL, USA). Data are the mean  $\pm$  standard deviation for con-

tinuous variables and as proportions for categorical variables. The chi-square test was used to determine differences in categorical variables between groups. Sensitivity was defined as the number of true-positive tests divided by the total number of patients with LVH as defined by echocardiography. Specificity was defined as the number of true-negative tests divided by the total number of patients who did not have LVH. The BNP level was log-transformed to achieve normality and correlation analyses undertaken. To evaluate the added discrimination provided by NT-proBNP levels to detect LVH beyond the information provided by ECG criteria, we compared the areas under the receiver-operator curves (ROCs) in models employing ECG criteria with and without NT-proBNP levels. Areas under ROC curves and the strength of the relationship were compared using MedCalc v11.0 (MedCalc, Mariakerke, Belgium). A two-sided  $P < 0.05$  was considered to be significant.

### Ethics statement

KoGES-ARIRANG was approved by the institutional review board of Wonju Christian Hospital, Wonju College of Medicine, Yonsei University (Wonju, Korea, approval number: CR105024). Written informed consent was obtained from all study participants.

## RESULTS

### Demographic and clinical characteristics

The demographic and clinical characteristics of the 343 subjects (mean age,  $52.8 \pm 7.9$  yr; 39.4% males) were reported according

to the presence of LVH (Table 1). The prevalence of LVH was 26.5% and was significantly higher in females (16.3% of males and 33.2% of females,  $P < 0.001$ ). Subjects with LVH were older and shorter compared with subjects who did not have LVH. Fasting blood glucose and triglyceride levels were significantly lower in the LVH group. The body mass index (BMI) was significantly higher in the LVH group ( $25.7 \pm 3.5$  vs.  $24.7 \pm 3.1$  kg/m<sup>2</sup>,  $P = 0.02$ ).

### Echocardiographic characteristics

The mean LVEF was  $65.4 \pm 6.5\%$ . In subjects with LVH, LVMI was  $117.8 \pm 19.2$  g/m<sup>2</sup>, and LV geometry showed enlarged LV dimensions ( $5.3 \pm 0.5$  vs.  $4.9 \pm 0.5$  cm,  $P < 0.001$ ) and thicker walls ( $0.36 \pm 0.08$  vs.  $0.33 \pm 0.06$ ,  $P = 0.02$ ) (Table 2). LVEF was not different according to the presence of LVH. The mitral E velocity was similar between groups, but the A velocity was increased in the LVH group ( $0.74 \pm 0.19$  vs.  $0.68 \pm 0.17$  m/s,  $P = 0.01$ ). As a result, the E/A ratio decreased ( $0.87 \pm 0.32$  vs.  $1.01 \pm 0.34$ ,  $P = 0.001$ ). TDI revealed an elevated E/E' ratio in the LVH group ( $10.6 \pm 5.6$  vs.  $7.7 \pm 5.4$ ,  $P < 0.001$ ).

### Characteristics and performance of ECG

ECG characteristics according to the presence of LVH are demonstrated in Table 3. The prevalence of LVH as defined by Sokolow-Lyon criteria and by the Cornell voltage criteria was 4.1% and 4.7%, respectively. ECG characteristics, including the Sokolow-Lyon voltage and Cornell voltage, were not significantly different regardless of LVH (Table 3). However, the Sokolow-Lyon voltage was correlated with the LVMI ( $r = 0.18$ ,  $P = 0.001$ ), as

**Table 1.** Demographic and clinical characteristics

Parameters	Without LVH (n = 252)	With LVH (n = 91)	P
Male, No. (%)	113 (44.8)	22 (24.2)	0.001
Age (yr)	$51.2 \pm 7.3$	$57.3 \pm 7.8$	< 0.001
Height (cm)	$160.8 \pm 8.6$	$156.0 \pm 8.0$	< 0.001
Weight (kg)	$64.0 \pm 10.2$	$62.6 \pm 10.4$	0.26
Waist circumference (cm)	$85.5 \pm 10.0$	$86.9 \pm 11.0$	0.26
Hip circumference (cm)	$96.3 \pm 8.4$	$97.7 \pm 6.2$	0.15
Body mass index (kg/m <sup>2</sup> )	$24.7 \pm 3.1$	$25.7 \pm 3.5$	0.02
History of hypertension, No. (%)	38 (15.1)	22 (24.2)	0.050
History of diabetes mellitus, No. (%)	18 (7.1)	7 (7.7)	0.86
History of dyslipidemia, No. (%)	18 (7.1)	2 (2.2)	0.08
Systolic blood pressure (mmHg)	$130.9 \pm 15.6$	$134.7 \pm 19.5$	0.11
Diastolic blood pressure (mmHg)	$81.6 \pm 12.2$	$82.0 \pm 11.5$	0.80
Glucose (mg/dL)	$97.8 \pm 20.2$	$93.6 \pm 13.1$	0.02
Total cholesterol (mg/dL)	$196.8 \pm 35.1$	$200.8 \pm 41.2$	0.38
HDL-cholesterol (mg/dL)	$45.2 \pm 11.4$	$45.3 \pm 10.2$	0.96
LDL-cholesterol (mg/dL)	$113.3 \pm 30.0$	$120.9 \pm 33.7$	0.045
Triglyceride (mg/dL)	$158.7 \pm 133.1$	$133.4 \pm 68.9$	0.02
Creatinine (mg/dL)	$0.95 \pm 0.15$	$0.88 \pm 0.12$	< 0.001
NT-proBNP (pg/mL)	$39.6 \pm 48.7$	$58.4 \pm 51.1$	< 0.01

LVH, left ventricular hypertrophy; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NT-proBNP, N-terminal pro-B-type natriuretic peptide. Data are the mean  $\pm$  SD, or N (%).

**Table 2.** Echocardiographic parameter

Parameters	Without LVH (n = 252)	With LVH (n = 91)	P
LA volume (mL)	$11.5 \pm 15.6$	$11.7 \pm 18.5$	0.94
LA volume index (mL/m <sup>2</sup> )	$6.8 \pm 9.1$	$7.0 \pm 11.1$	0.86
IVSd (cm)	$0.8 \pm 0.1$	$0.9 \pm 0.1$	< 0.001
LVPWd (cm)	$0.8 \pm 0.1$	$0.9 \pm 0.2$	< 0.001
LVDd (cm)	$4.9 \pm 0.5$	$5.3 \pm 0.5$	< 0.001
Relative wall thickness	$0.33 \pm 0.06$	$0.36 \pm 0.08$	0.02
Ejection fraction (%)	$65.7 \pm 6.2$	$64.7 \pm 6.5$	0.19
LV mass/BSA (g/m <sup>2</sup> )	$81.6 \pm 14.4$	$117.8 \pm 19.2$	< 0.001
E (m/s)	$0.67 \pm 0.19$	$0.64 \pm 0.19$	0.13
A (m/s)	$0.68 \pm 0.17$	$0.74 \pm 0.19$	0.01
Deceleration time (ms)	$212.2 \pm 60.5$	$214.6 \pm 52.6$	0.74
E/A	$1.01 \pm 0.34$	$0.87 \pm 0.32$	0.001
E' (cm/s)	$0.05 \pm 0.05$	$0.04 \pm 0.02$	0.06
A' (cm/s)	$0.07 \pm 0.04$	$0.07 \pm 0.04$	0.63
E/E'	$7.7 \pm 5.4$	$10.6 \pm 5.6$	< 0.001

LVH, left ventricular hypertrophy; LA, left atrium; IVSd, end-diastolic interventricular septal thickness; LVPWd, end-diastolic left ventricular posterior wall thickness; LVDd, end-diastolic left ventricular dimension; LV, left ventricle; BSA, body surface area; E, peak early diastolic transmitral flow velocity; A, peak late diastolic transmitral flow velocity; E/A, ratio of peak early to late diastolic transmitral flow velocity; E', peak early diastolic mitral annular velocity; A', peak late diastolic mitral annular velocity; E/E', ratio of peak early diastolic transmitral flow velocity to peak early diastolic mitral annular velocity. Data are the mean  $\pm$  SD.

was the Cornell voltage ( $r = 0.16$ ,  $P = 0.003$ ). The strengths of the relationships were not significantly different for ECG criteria with the LVMI ( $P = 0.83$ ) (Table 4). The performance of the tested ECG criteria for the echocardiographic diagnosis of LVH was assessed in terms of sensitivity and specificity (Table 5). Both ECG criteria showed low sensitivity and high specificity. The Sokolow-Lyon criteria had 3.3% sensitivity, 95.6% specificity, 21.4% positive predictive value, and 73.3% negative predictable value. The criteria for the Cornell voltage had a sensitivity of 6.6%, a specificity of 99.2%, a positive predictive value of 37.5%, and a negative predictable value of 74.0%. The accuracy of the Sokolow-Lyon criteria was 71.1% and that of the Cornell voltage

criteria was 72.3%.

### Characteristics of NT-proBNP and combined test performance

The mean level of NT-proBNP was  $44.6 \pm 49.9$  pg/mL, which was significantly higher in subjects with LVH ( $58.4 \pm 51.1$  vs.  $39.6 \pm 48.7$  pg/mL,  $P < 0.01$ ) (Table 1). The NT-proBNP level was correlated with the LVMI ( $r = 0.17$ ,  $P = 0.002$ ). The strengths of relationships were similar for the BNP level and for ECG cri-

**Table 3.** Electrocardiographic characteristics

Parameters	Without LVH (n = 252)	With LVH (n = 91)	P
PR interval (ms)	160.6 ± 24.2	156.8 ± 27.6	0.06
QRS duration (ms)	90.1 ± 12.3	90.7 ± 14.7	0.70
QTc (ms)	425.4 ± 24.1	429.4 ± 21.5	0.16
SV1 (mm)	5.8 ± 4.5	5.7 ± 4.8	0.90
RV5 (mm)	11.2 ± 6.7	10.4 ± 8.4	0.40
RV6 (mm)	1.9 ± 2.5	1.8 ± 2.5	0.84
SV3 (mm)	2.7 ± 3.0	2.0 ± 2.6	0.054
SV1+RV5 (mm)	21.7 ± 6.2	23.4 ± 6.7	0.03
SV1+RV6 (mm)	19.9 ± 5.9	21.0 ± 5.6	0.11
Sokolow-Lyon voltage (mm)	22.1 ± 6.1	23.4 ± 6.7	0.09
Cornell voltage (mm)	12.6 ± 5.6	13.1 ± 5.5	0.48
Sokow-Lyon criteria LVH (%)	11 (4.4)	3 (3.3)	0.67
Cornell voltage criteria LVH (%)	10 (4.0)	6 (6.6)	0.41

LVH, left ventricular hypertrophy; QTc, corrected QT interval; SV1, S wave amplitude in V1 lead; RV5, R wave amplitude in V5 lead; RV6, R wave amplitude in V6 lead; SV3, S wave amplitude in V3 lead. Data are the mean ± SD, or N (%).

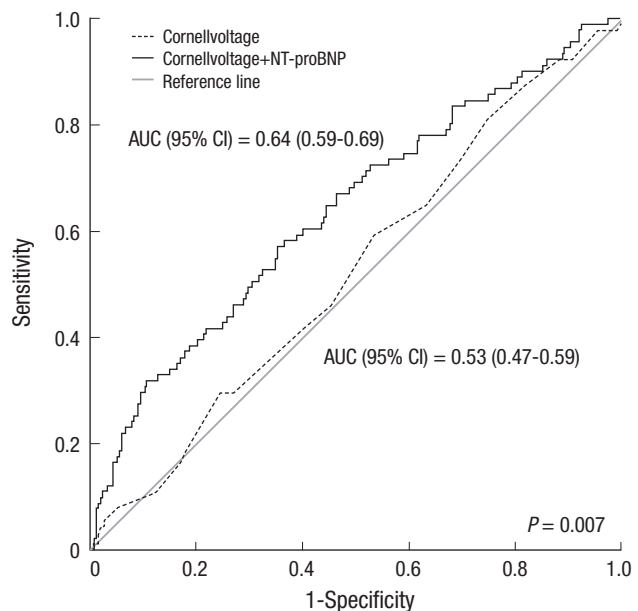
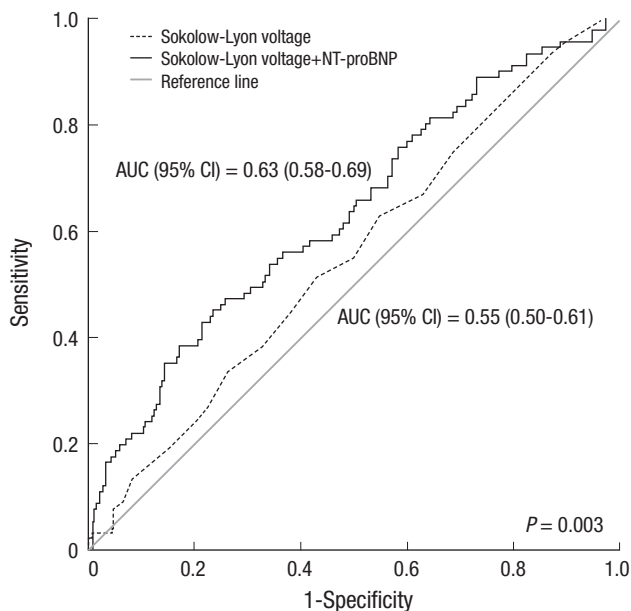
**Table 4.** Relationship between electrocardiographic criteria and NT-proBNP levels to left ventricular hypertrophy

Variables	LVH <i>r</i> (95% confidence interval)
Sokolow-Lyon voltage	0.18 (0.07-0.28)
Cornell voltage	0.16 (0.05-0.26)
Log NT-proBNP	0.17 (0.06-0.27)
<i>P</i> value, Sokolow-Lyon voltage vs. Cornell voltage	0.83
<i>P</i> value, Sokolow-Lyon voltage vs. log NT-proBNP	0.39
<i>P</i> value, Cornell voltage vs. log NT-proBNP	0.52

NT-proBNP, N-terminal pro-B-type natriuretic peptide. Correlations compared by the Z statistic.

**Table 5.** Diagnostic performance of electrocardiographic left ventricular hypertrophy criteria

Diagnostic values	Sokolow-Lyon criteria	Cornell voltage criteria
Sensitivity (%)	3.3	6.6
Specificity (%)	95.6	96.0
Positive predictive value (%)	21.4	37.5
Negative predictable value (%)	73.3	74.0
Accuracy (%)	71.1	72.3



**Fig. 1.** Receiver operating characteristic (ROC) curves for the combination of N-terminal pro-B-type natriuretic peptide (NT-proBNP) level and electrocardiography (ECG) criteria compared with ECG criteria alone for the detection of left ventricular hypertrophy.

teria with the LVMI (Table 4). The area under the ROC to detect LVH was 0.55 (95% confidence interval [CI], 0.50-0.61) using the Sokolow-Lyon criteria and 0.53 (0.47-0.59) using the Cornell voltage criteria. After adding NT-proBNP levels to the model, the corresponding areas under the ROC were 0.63 (0.58-0.69) and 0.64 (0.59-0.69), respectively. *P*-values for the comparison in areas under the ROC for models with and without NT-proBNP levels were  $< 0.001$  (Fig. 1).

## DISCUSSION

The present study evaluated the diagnostic performance of NT-proBNP levels when added to ECG criteria for the detection of LVH in a Korean community-based population. This study demonstrated the low sensitivity and high specificity of ECG criteria. Overall, the area under the curve (AUC) for both ECG criteria for the detection of LVH was  $\leq 0.61$ , which severely limits the potential of using ECG as a screening tool for LVH. Addition of NT-proBNP levels to ECG criteria improved discriminating power for the detection of LVH in our general population.

LVH has been shown to be an independent risk factor for adverse cardiovascular events (3, 27). As such, early identification of LVH patients is critical for risk stratification. Given its low cost, availability and prognostic significance, ECG is recommended to be the diagnostic screening method for evaluation of LVH (28). However, studies have shown the median sensitivity to range from 15% (range, 2%-41%) for the Cornell voltage criteria to 21% (4%-52%) for the Sokolow-Lyon index. The median specificity has been reported to range from 89% (53%-100%) for the Sokolow-Lyon index to 96% (91%-100%) for the Cornell voltage criteria (29). However, data evaluating the accuracy of ECG criteria for the detection of LVH in Korea are limited. In a small study conducted in Korea, the sensitivity and specificity of the Sokolow-Lyon index were found to be 11.3% and 95.5% and those of the Cornell voltage criteria to be 1.4% and 100%, respectively (30). The present study is the first to evaluate the accuracy of ECG criteria in a Korean general population. We demonstrated the low sensitivity and high specificity of ECG criteria. Irrespective of the index used, ECG was a poor screening tool for the diagnosis of LVH.

LVH is a compensatory response of the myocardium to maintain normal cardiac function in response to pressure overload and other various stimuli (31). The growth and composition of the myocardium are altered by locally produced neurohormones such as noradrenaline, angiotensin II, aldosterone, endothelin and bradykinin which, in addition to their hemodynamic effects, act directly as growth factors (32-34). Myocardial growth resulting from the increased size and protein content of myocytes is paralleled by progressive expansion of interstitial fibroblast compartments and enhanced deposition of collagen. These adaptive responses allow the heart to withstand the increased

intracardiac pressures associated with overload, and increased interstitial collagen leads to reduced LV compliance, leading to diastolic dysfunction (31). Eventually, synthesis of ventricular natriuretic peptide is re-induced, and the activated natriuretic peptide system may act as a counter-regulatory mechanism against further hypertrophy. In the present study, LVH was associated with diastolic dysfunction and NT-proBNP levels were well correlated with the LVMI and  $E/E'$ . Several authors have reported on the use of BNP for the community screening of LVH, but consensus is lacking on the diagnostic performance of BNP levels. In the Framingham Heart Study, the AUC of BNP levels for the detection of elevated LV mass was 0.72 in males and 0.57 in females (11). In the Fourth Copenhagen City Heart Study, the diagnostic performance of NT-proBNP levels for the detection of LVH was 0.70 (0.66-0.74) and 0.63 (0.59-0.68) for females and males, respectively (35). In the Dallas Heart Study, investigators evaluated a multimarker strategy to improve the diagnostic performance for LVH screening. They reported that better screening could be achieved by a combination of ECG as well as levels of troponin I and NT-proBNP (AUC, 0.798 [95% CI, 0.754-0.842]), which collectively provide additional information compared with ECG alone (36). In the present study, addition of NT-proBNP level to ECG criteria improved the diagnostic performance expressed as AUC values from ROC curves compared with ECG criteria only, but the value of AUC was  $< 0.7$ . Thus, addition NT-proBNP levels to ECG criteria seem to be suboptimal for diagnostic LVH screening.

Our community-based cohort reduced the possibility of spectrum bias, whereas evaluation of all subjects with both echocardiography and NT-proBNP levels eliminated verification bias. Nevertheless, the present study had important limitations. The sample size was relatively small compared with other cohort studies. It could be argued that echocardiography is an imperfect "gold standard" for the diagnosis of LVH. The cutoff value of LVH was defined by recommendations from the American Society of Echocardiography, but this cutoff value may be different in a Korean general population. Most echocardiographic data are derived from western countries but, because racial differences can influence the size and function of cardiac chambers, evaluation of the echocardiographic parameters in racial populations (37-39). There are limited data for the reference values of cardiac geometry in Asian populations. In the Japanese Normal Values for Echocardiographic Measurements Project (JAMP) study, the reference values for the LVMI were  $76 \pm 16$  g/m<sup>2</sup> in males and  $70 \pm 14$  g/m<sup>2</sup> in females (40). According to those results, the LVMI was small in Asian populations compared with Western populations. Also, the present study was a cross-sectional cohort study, and the prognostic significances of LVH and NT-proBNP levels were not evaluated.

In conclusion, our community-based study demonstrated that the sensitivity of ECG criteria was low and the power to rule

in LVH was unsatisfactory, and that ECG cannot be considered a screening test for the diagnosis of LVH. Addition of NT-proBNP levels to ECG criteria for the detection of LVH improved the discriminating power but was suboptimal, suggesting limited usefulness as a mass screening tool. Further large-scale research is needed to identify the cutoff value for the diagnosis of LVH in Korean populations, and to develop alternative diagnostic methods for the assessment of LVH in community screening.

## DISCLOSURE

The authors have no conflicts of interest to disclose.

## AUTHOR CONTRIBUTION

Conception and coordination of the study: Yoo BS, Ahn MS. Design of ethical issues: Park JK, Ahn SV, Kim JY. Acquisition of data: Park JK, Ahn SV. Data review: Ahn MS, Kim JY, Yoo BS. Statistical analysis: Choi EH, Ahn MS. Manuscript preparation: Ahn MS, Yoo BS, Lee JH, Lee JW, Youn YJ, Ahn SG, Kim JY, Lee SH, Yoon JH. Manuscript approval: all authors.

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## REFERENCES

- Kannel WB, Gordon T, Offutt D. Left ventricular hypertrophy by electrocardiogram. Prevalence, incidence, and mortality in the Framingham study. *Ann Intern Med* 1969; 71: 89-105.
- Kannel WB, Gordon T, Castelli WP, Margolis JR. Electrocardiographic left ventricular hypertrophy and risk of coronary heart disease. The Framingham study. *Ann Intern Med* 1970; 72: 813-22.
- Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Gattobigio R, Zampi I, Porcellati C. Prognostic value of a new electrocardiographic method for diagnosis of left ventricular hypertrophy in essential hypertension. *J Am Coll Cardiol* 1998; 31: 383-90.
- Sundström J, Lind L, Arnlöv J, Zethelius B, Andrén B, HO. L. Echocardiographic and electrocardiographic diagnoses of left ventricular hypertrophy predict mortality independently of each other in a population of elderly men. *Circulation* 2001; 103: 2346-51.
- Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, et al.; ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003; 361: 1149-58.
- Woythaler JN, Singer SL, Kwan OL, Meltzer RS, Reubner B, Bommer W, DeMaria A. Accuracy of echocardiography versus electrocardiography in detecting left ventricular hypertrophy: comparison with postmortem mass measurements. *J Am Coll Cardiol* 1983; 2: 305-11.
- Soeki T, Kishimoto I, Okumura H, Tokudome T, Horio T, Mori K, Kangawa K. C-type natriuretic peptide, a novel antifibrotic and antihypertrophic agent, prevents cardiac remodeling after myocardial infarction. *J Am Coll Cardiol* 2005; 45: 608-16.
- Choi SY, Lee JE, Jang EH, Kim MO, Baek H, Ki CS, Park SW, Kim DJ, Huh WS, Oh HY, et al. Association between changes in N-terminal pro-brain natriuretic peptide levels and changes in left ventricular mass index in stable hemodialysis patients. *Nephron Clin Pract* 2008; 110: c93-100.
- Wang AY, Lam CW, Wang M, Chan IH, Lui SF, Zhang Y, Sanderson JE. Diagnostic potential of serum biomarkers for left ventricular abnormalities in chronic peritoneal dialysis patients. *Nephrol Dial Transplant* 2009; 24: 1962-9.
- Luchner A, Burnett JC Jr, Jougasaki M, Hense HW, Heid IM, Muders F, Riegger GA, Schunkert H. Evaluation of brain natriuretic peptide as marker of left ventricular dysfunction and hypertrophy in the population. *J Hypertens* 2000; 18: 1121-8.
- Vasan RS, Benjamin EJ, Larson MG, Leip EP, Wang TJ, Wilson PW, Levy D. Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction: the Framingham heart study. *JAMA* 2002; 288: 1252-9.
- Ahn MS, Kim JY, Youn YJ, Kim SY, Koh SB, Lee K, Yoo BS, Lee SH, Yoon J, Park JK, et al. Cardiovascular parameters correlated with metabolic syndrome in a rural community cohort of Korea: the ARIRANG study. *J Korean Med Sci* 2010; 25: 1045-52.
- Koh SB, Park JK, Yoon JH, Chang SJ, Oh SS, Kim JY, Ryu SY, Kim KS, Lee TY, You JS. Preliminary report: a serious link between adiponectin levels and metabolic syndrome in a Korean nondiabetic population. *Metabolism* 2010; 59: 333-7.
- Koh SB, Yoon J, Kim JY, Yoo BS, Lee SH, Park JK, Choe KH. Relationships between serum adiponectin with metabolic syndrome and components of metabolic syndrome in non-diabetic Koreans: ARIRANG study. *Yonsei Med J* 2011; 52: 234-41.
- Lee JH, Kim JY, Kim KM, Lee JW, Youn YJ, Ahn MS, Yoo BS, Lee SH, Yoon J, Choe KH, et al. A prospective study of epicardial adipose tissue and incident metabolic syndrome: the ARIRANG study. *J Korean Med Sci* 2013; 28: 1762-7.
- Kim JY, Ahn SV, Yoon JH, Koh SB, Yoon J, Yoo BS, Lee SH, Park JK, Choe KH, Guallar E. Prospective study of serum adiponectin and incident metabolic syndrome: the ARIRANG study. *Diabetes Care* 2013; 36: 1547-53.
- Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, et al.; Chamber Quantification Writing Group; American Society of Echocardiography's Guide-

- lines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; 18: 1440-63.
18. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989; 2: 358-67.
  19. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986; 57: 450-8.
  20. Quiñones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA; Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr* 2002; 15: 167-84.
  21. Dumesnil JG, Paulin C, Pibarot P, Coulombe D, Arsenaault M. Mitral annulus velocities by Doppler tissue imaging: practical implications with regard to preload alterations, sample position, and normal values. *J Am Soc Echocardiogr* 2002; 15: 1226-31.
  22. Sohn DW, Chai IH, Lee DJ, Kim HC, Kim HS, Oh BH, Lee MM, Park YB, Choi YS, Seo JD, et al. Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. *J Am Coll Cardiol* 1997; 30: 474-80.
  23. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. *Am Heart J* 1949; 37: 161-86.
  24. Casale PN, Devereux RB, Alonso DR, Campo E, Kligfield P. Improved sex-specific criteria of left ventricular hypertrophy for clinical and computer interpretation of electrocardiograms: validation with autopsy findings. *Circulation* 1987; 75: 565-72.
  25. Fradley MG, Larson MG, Cheng S, McCabe E, Coglianese E, Shah RV, Levy D, Vasan RS, Wang TJ. Reference limits for N-terminal-pro-B-type natriuretic peptide in healthy individuals (from the Framingham Heart Study). *Am J Cardiol* 2011; 108: 1341-5.
  26. Karl J, Borgya A, Gallusser A, Huber E, Krueger K, Rollinger W, Schenk J. Development of a novel, N-terminal-proBNP (NT-proBNP) assay with a low detection limit. *Scand J Clin Lab Invest Suppl* 1999; 230: 177-81.
  27. Jissho S, Shimada K, Taguchi H, Yoshida K, Fukuda S, Tanaka H, Yoshikawa J, Yoshiyama M, Ishii M, Goto Y. Impact of electrocardiographic left ventricular hypertrophy on the occurrence of cardiovascular events in elderly hypertensive patients. - The Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). *Circ J* 2010; 74: 938-45.
  28. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, et al.; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; 289: 2560-72.
  29. Pewsner D, Jüni P, Egger M, Battaglia M, Sundström J, Bachmann LM. Accuracy of electrocardiography in diagnosis of left ventricular hypertrophy in arterial hypertension: systematic review. *BMJ* 2007; 335: 711.
  30. Park JK, Shin JH, Kim SH, Lim YH, Kim KS, Kim SG, Kim JH, Lim HG, Shin J. A comparison of cornell and sokolow-lyon electrocardiographic criteria for left ventricular hypertrophy in korean patients. *Korean Circ J* 2012; 42: 606-13.
  31. Frey N, Olson EN. Cardiac hypertrophy: the good, the bad, and the ugly. *Annu Rev Physiol* 2003; 65: 45-79.
  32. Paradis P, Dali-Youcef N, Paradis FW, Thibault G, Nemer M. Overexpression of angiotensin II type I receptor in cardiomyocytes induces cardiac hypertrophy and remodeling. *Proc Natl Acad Sci U S A* 2000; 97: 931-6.
  33. Kaye D, Esler M. Sympathetic neuronal regulation of the heart in aging and heart failure. *Cardiovasc Res* 2005; 66: 256-64.
  34. Rizvi MA, Katwa L, Spadone DP, Myers PR. The effects of endothelin-1 on collagen type I and type III synthesis in cultured porcine coronary artery vascular smooth muscle cells. *J Mol Cell Cardiol* 1996; 28: 243-52.
  35. Goetze JP, Mogelvang R, Maage L, Scharling H, Schnohr P, Sogaard P, Rehfeld JF, Jensen JS. Plasma pro-B-type natriuretic peptide in the general population: screening for left ventricular hypertrophy and systolic dysfunction. *Eur Heart J* 2006; 27: 3004-10.
  36. Martinez-Rumayor AA, de Lemos JA, Rohatgi AK, Ayers CR, Powell-Wiley TM, Lakoski SG, Berry JD, Khera A, Das SR. Addition of highly sensitive troponin T and N-terminal pro-B-type natriuretic peptide to electrocardiography for detection of left ventricular hypertrophy: results from the Dallas Heart Study. *Hypertension* 2013; 61: 105-11.
  37. Wong CY, O'Moore-Sullivan T, Leano R, Byrne N, Beller E, Marwick TH. Alterations of left ventricular myocardial characteristics associated with obesity. *Circulation* 2004; 110: 3081-7.
  38. Hinderliter AL, Light KC, Willis PW 4th. Racial differences in left ventricular structure in healthy young adults. *Am J Cardiol* 1992; 69: 1196-9.
  39. Harshfield GA, Koelsch DW, Pulliam DA, Alpert BS, Richey PA, Becker JA. Racial differences in the age-related increase in left ventricular mass in youths. *Hypertension* 1994; 24: 747-51.
  40. Daimon M, Watanabe H, Abe Y, Hirata K, Hozumi T, Ishii K, Ito H, Iwakura K, Izumi C, Matsuzaki M, et al. Normal values of echocardiographic parameters in relation to age in a healthy Japanese population: the JAMP study. *Circ J* 2008; 72: 1859-66.