（表紙）

表　　題　日本人の高齢高血圧患者における心電図上の左室肥大と心血管疾患との関連

論 文 の 区 分　博士課程

著　　者　　名　エイジロ　スギヤマ　エヂソン

担当指導教員氏名　教授　苅尾　七臣

所　　属　自治医科大学大学院医学研究科
地域医療学系 専攻
循環器・呼吸器疾患分野
心血管病学

2015 年 1 月 9 日申請の学位論文

Association of Electrocardiographic Left Ventricular Hypertrophy with Incident Cardiovascular Disease in Japanese Older Hypertensive Patients

by

Eijiro Sugiyama Edison

Submitted in accordance with the requirements for the degree of Doctor of Philosophy in Cardiovascular Medicine

Jichi Medical University
School of Medicine
January 2015

Content

1. Introduction

In one of the very early reports from the Framingham Heart Study, three main risk factors for cardiovascular disease (CVD) morbidity and mortality were revealed: hypertension, hypercholesterolemia, and left ventricular hypertrophy (LVH).[1] LVH was defined as increased left ventricular mass due to ventricular dilatation, wall thickening, or a combination of ventricular dilatation and wall thickening. Its assessment by standard 12-lead electrocardiography (ECG) or echocardiography was found to be associated with a higher risk of CVD morbidity and mortality in general populations[2,3] and hypertensive patients.[4,5] The LVH-CVD association was independent of traditional cardiovascular risk factors such as age, high blood pressure (BP), diabetes mellitus, and obesity.[6] Although LVH has been shown to be an independent predictor of clinical outcomes, the reasons behind the robust association between LVH and CVD morbidity and mortality have been unclear.

1.1. The Pathophysiology of LVH

The pathogenesis of LVH increases progressively with age and involves many factors including mechanical forces/pressure overload, neurohumoral activity, hemostatic factors, genetic factors, inflammatory mediators, and metabolic abnormalities, which together lead to a complex molecular mechanism.[7] The contributions of these factors alone and in combination extend to cardiac hypertrophy and remodeling through the impairment of cardiac myocytes, fibroblast proliferation, collagen synthesis and apoptosis.[8] Hemodynamic factors (i.e., pressure load) and nonhemodynamic factors (e.g., neurohumoral activity and abnormal hemostatic factors) were proposed as critical determinant issues of LVH.

1.1.1. Hemodynamic Factors

According to Laplace's Law, afterload that induces an elevation of systolic wall stress and oxygen consumption enhance the ventricular wall thickness as a compensatory mechanism to reduce wall stress.[9] The hypertrophy caused by the hemodynamic burden could lead to adapted (physiological) or maladapted (pathological) hypertrophy. Physiological hypertrophy is created by a transient hemodynamic overload such as the overloads that occur with pregnancy or regular exercise activity. Pathological hypertrophy is caused by a chronic hemodynamic overload. Several conditions can enable pathological hypertrophy, such as a pressure overload (systemic hypertension and aortic stenosis) which leads to concentric LVH, and a volume overload (chronic aortic regurgitation or mitral valve regurgitation) which leads to eccentric LVH.[10,11]

Both hypertension and aortic stenosis enhances the pressure load of the left ventricle. Increased pressure on the intraventricular area in hypertension and aortic stenosis will lead to structural remodeling of the heart such as myocytic hypertrophy, increased perimyocytic fibrosis, and myocardial scarring. However, hypertension, not aortic stenosis, is also accompanied by intramyocardial arteriole wall thickening and increased perivascular fibrosis.[12] This might explain the discrepancy in the morphology and histology pattern of LVH between hypertension and aortic stenosis, although each has the same burden of afterload on the left ventricle. Hence, hypertension has a more destructive effect on target organs, leading to unfavorable clinical outcomes.

Blood pressure has an important part in the hemodynamic burden of LVH. The prevalence of LVH has been found to be higher in hypertensive individuals compared to normotensive patients. For example, Hammond *et al.* [13] showed that the prevalence of LVH was 12% in borderline hypertensive patients and 20% in patients with mild, uncomplicated sustained

essential hypertension. In the Framingham Heart Study, the risks of LVH in patients with normal BP (systolic BP [SBP] < 140 mmHg), mild hypertension (SBP 140 – 160 mmHg) and severe hypertension (SBP > 180 mmHg) were found to be 2%, 6%, and 19%, respectively.[11] BP *per se* is a hemodynamic phenomenon that varies from moment to moment over a 24-hour day, characterized by a dip BP pattern during the night followed by a surge BP pattern in the early morning. However, BP fluctuations not only between sleep and awake periods but also from minute to minute are induced by human behavior, including neurohumoral activity.[14,15] It is well known that out-of-office BP is more strongly associated with target organ damage than conventional BP taken in a clinician's office, since cardiac hypertrophy it self is a reflection of time-integrated and chronic exposure to high BP that cannot be represented by only a single clinic BP measurement.[16] In particular, higher 24-hour BP and higher nocturnal BP have been shown to be associated with LVH in hypertensive patients.[17-19]

We performed the Japan Morning Surge-Target Organ Protection (J-TOP) Study, an open-label randomized multicenter trial using the stratified allocation of hypertensive patients based on morning and evening differences in their home BP values.[20] In the J-TOP study, the titration was guided not by doctor-measured office BP but by home BP self-measured using a memory-equipped device to compare the morning or bedtime dosing of candesartan (plus a diuretic if needed) among individuals with home SBP higher than 135 mmHg. We observed and investigated the ECG-LVH changes from baseline (0 month) compared with the values at a 6 month follow-up using the Cornell voltage and Sokolow-Lyon voltage criteria during antihypertension treatment (n=235, mean age 63.5 yrs, 45% male). The results showed that reductions of office and home BP were followed by the regression of ECG-LVH (Figs. 1, 2). In addition, reductions in morning and night time home BP were significantly correlated with the

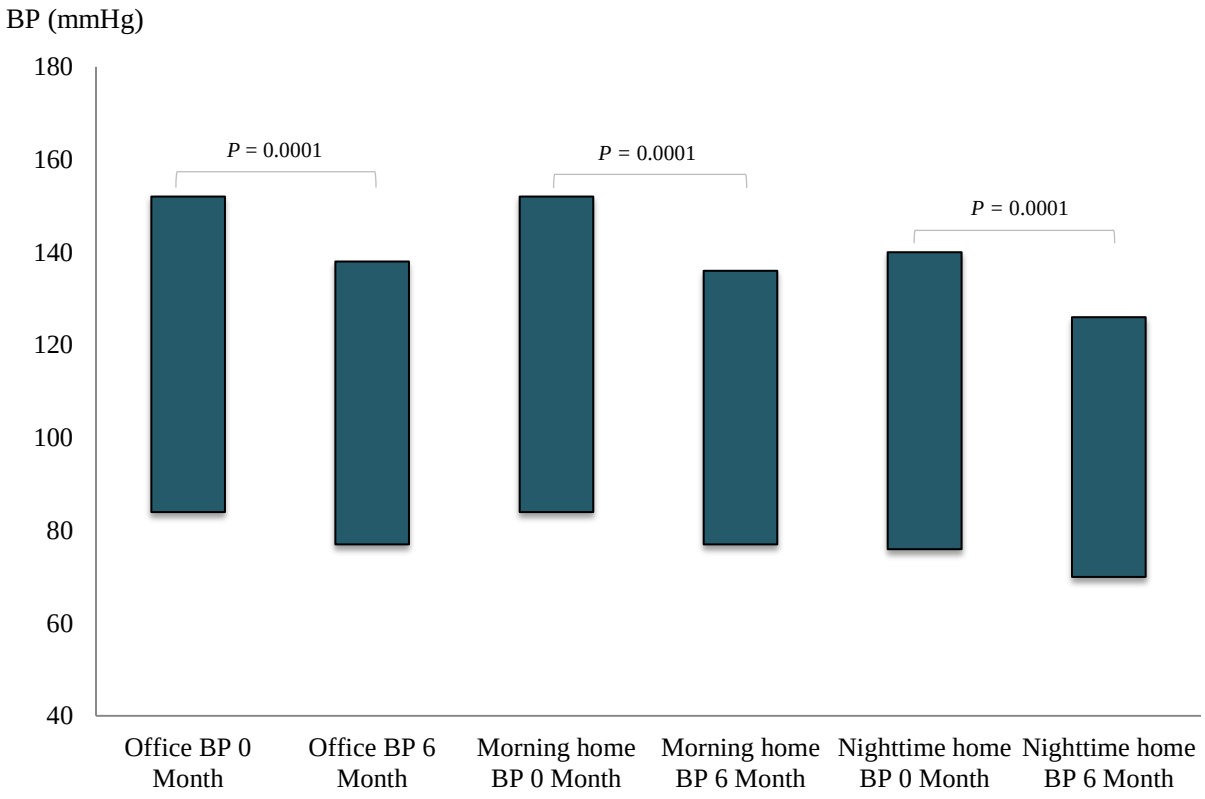


Figure 1. Office BP, Morning home BP, and Nighttime home BP of baseline and 6 month follow-up therapy in the J-TOP study (unpublished data). Abbreviations: BP, Blood pressure.

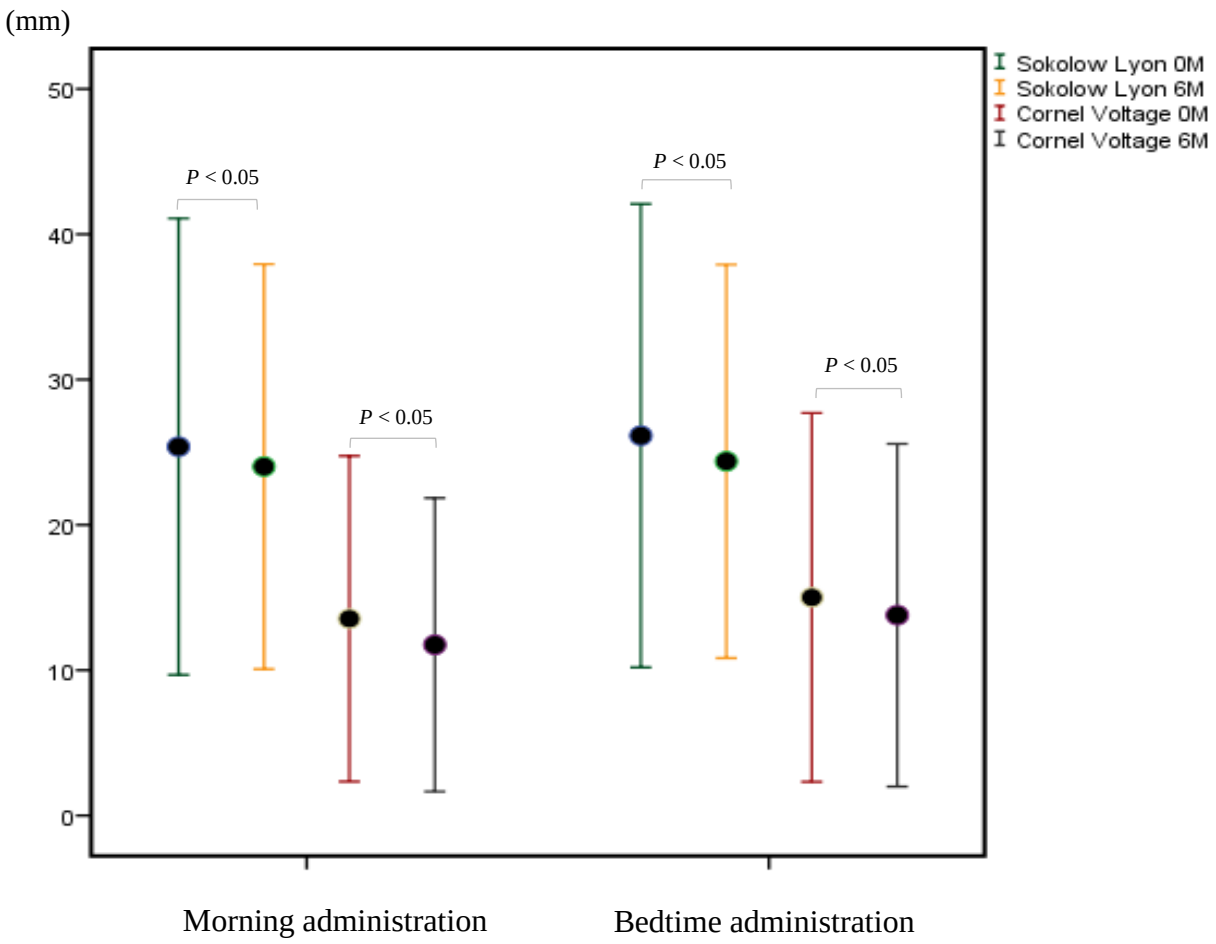


Figure 2. Sokolow-Lyon and Cornell voltage LVH of baseline and 6 month follow-up therapy in the J-TOP study (unpublished data).

Table 1. Univariate correlations between reductions in ECG-LVH criteria and reductions in BP parameters in the J-TOP study (unpublished data)

Δ ECG-LVH criteria	Δ Office SBP		Δ Home SBP (Morning)		Δ Home SBP (Nighttime)	
	r	*p*	*r*	*p*	*r*	*p*
Sokolow-Lyon	0.03	0.62	0.95	0.14	0.10	0.12
Cornell Voltage	0.83	0.22	0.22	0.001	0.21	0.001

Correlations were assessed by the Pearson's *r* coefficient. Abbreviations: BP, Blood pressure; ECG, Electrocardiography; LVH, Left ventricular hypertrophy; SBP, Systolic blood pressure

reduction of Cornell voltage LVH (Table 1). Thus, our findings confirmed the importance of out-of-office BP on hypertension-related target organ damage.

1.1.2. Nonhemodynamic Factors

The pathogenesis of LVH is not related solely to pressure-dependent phenomena such as increased pressure load and total peripheral resistance imposed by hypertension. Clinical studies suggested that even though LVH is closely associated with BP (particularly ambulatory BP), approx. 50% of the variance of LVH remains unexplained.[17] This may indicate that BP-independent mechanisms contribute to the development of LVH. Several nonhemodynamic factors are known to be involved in hypertrophy of the myocardium (including neurohumoral and hemostatic factors), independent of systemic arterial pressure.

1.1.2.1. Neurohumoral Factors

Many years ago, animal studies showed that sympathetic nerve activity (SNA) played a pivotal role in the development and progression of LVH[21] through the stimulation of myocardial β-adrenergic receptors.[22] The evidence was extended in human studies, which showed that SNA in hypertensive patients not only contributes to rising BP,[23] but also shows trophic properties.[24-26] Greenwood *et al.*[24] demonstrated that SNA assessed by peripheral muscle nerve activity was significantly higher in individuals with echocardiographic evidence of LVH compared to those without LVH. Schlaich *et al.*[25] showed that even though they had similar BP levels, hypertensive patients with LVH exhibited significantly higher cardiac norepinephrine spillover compared to hypertensive patients without LVH. Moreover, the cause-effect relationship between SNA and LVH is supported by the finding that the arterial noradrenaline level can be used to predict the left ventricular mass and the occurrence of LVH in patients who became hypertensive during a 20-year follow-up period, independent of their systolic BP and body mass index values.[26]

The pathological mechanism between increased neurohumoral activity and LVH is related to the direct influence of SNA on the volume of myocytes, vascular distensibility, the replication of vascular smooth muscle cells, and collagen synthesis.[27] SNA also indirectly favors cardiac hypertrophy through its effect on 24-hour BP variability (particularly during the daytime) and increases blood viscosity.[15,28] In addition, there is some evidence suggesting the contribution of other neurohormones, such as the effect of the renin angiotensin aldosterone system (RAAS) on the development of LVH. Koga *et al.*[29] showed that plasma renin activity (PRA; a marker of RAS activity) was significantly associated with ECG-LVH. Malmqvist *et al.*[30] observed that PRA and serum aldosterone were high in hypertensive patients with LVH compared to hypertensive patients without LVH. Lastly, plasma aldosterone was found to be significantly associated with LV mass in hypertensive patients with high fibrinogen levels independent of their office BP values, indicating an interaction of plasma aldosterone and fibrinogen in the development of LVH in hypertensive patients.[31]

1.1.2.2. Hemostatic Factors

The main complications of hypertension such as stroke and myocardial infarction are thrombotic rather than hemorrhagic, even though the vessel walls are exposed to high pressure in hypertensive patients.[32] It was shown that LVH as a higher risk complications of hypertension had abnormalities of hemostatic factors such as elevations of prothrombin fragment 1+2 (F1+2) and fibrinogen levels, in keeping with the well-known Virchow's triad (i.e., abnormalities of vessel wall, abnormalities of blood constituents, and abnormalities of blood flow).[33,34] The results of the Strong Heart Study suggested that in a population free of clinically overt coronary heart disease, elevated plasma fibrinogen was associated with echocardiographic LVH independent of significant covariates such as hypertension, diabetes, body size, antihypertensive

treatment, and renal dysfunction.[35] Moreover, abnormalities of plasminogen activator inhibitor[36] (PAI-1, an index of fibrinolysis) and von Willebrand factor[37] (vWF, a marker of endothelial dysfunction) which lead to impaired blood flow and increased shear stress, were shown to be associated with LV mass in hypertensive patients.

These factors may have important roles in thromboembolic evidence in individuals with hypertensive LVH. However, the relationships between various abnormal hemostatic factors and LVH are not yet completely understood. One possible explanation is that fibrinogen have a proinflammatory effect mediated by the modulation of myocyte apoptosis and the release of cytokines,[38] and that inflammation is activated in LVH.[39] Moreover, it was found that increased plasma fibrinogen altered the hemorheologic effect on the local and systemic circulation by increasing the blood viscosity, modifying endothelial cells, and increasing the shear stress of the vascular wall.[40] Thus, increased plasma fibrinogen will add an unfavorable burden via an increase in the cardiac workload.

1.2. The Diagnosis of LVH

LVH can now be assessed by many different methods, including ECG, M-mode echocardiography, 2D echocardiography, 3D echocardiography, and more recently by cardiac MRI. Each of these methods has its specific values of sensitivity, specificity, availability and cost. Clinical studies showed that both cardiac MRI and echocardiography have a greater ability to detect LVH due to their relatively high sensitivity, whereas ECG showed low sensitivity.[41] However, in daily clinical practice the use of ECG is common for diagnostic procedures because it is easy to perform, relatively simple, widely available, and low-cost. The results of two large cohort trials, the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE)[42,43] and

the Heart Outcome Prevention Evaluation (HOPE)[44], confirmed that the regression of LVH assessed by ECG during antihypertensive therapy results in improved outcomes, independent of BP reduction.

ECG also provides additional data of clinical relevance that are associated with worse prognoses such as signs of cardiac overload, strain or ischemia, and arrhythmias.[45] Indeed, current guidelines issued by the European Society of Hypertension and the European Society of Cardiology (ESH/ESC 2013)[46] and the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014)[47] still recommend ECG as a first-line routine examination for LVH screening, especially in hypertensive patients.

2. Objectives

Although it has been established that there is an association between LVH and CVD, it is not yet clear whether ECG-LVH in hypertensive patients is associated with a higher risk of CVD events, independently of 24-hour BP (including nocturnal BP), SNA, and hemostatic factors. In the present study of elderly hypertensive patients, we assessed whether ECG-LVH is associated with incident CVD events independently of 24-hour BP including nocturnal BP. We also assessed whether ECG-LVH is associated with incident CVD events, independently of circulating levels of norepinephrine and hemostatic factors (i.e., fibrinogen, F1+2, vWF, and PAI-1) in older hypertensive patients.

3. Methods

3.1. Subjects

The methods the Jichi Medical School Ambulatory Blood Pressure Monitoring (JMS-ABPM) Wave 1 study have been detailed elsewhere.[48-51] Briefly, we enrolled 821 hypertensive

outpatients (office BP ≥ 140/90 mmHg or antihypertensive medication use) > 50 years of age. These patients were recruited from 6 institutions (3 clinics, 2 hospitals, and 1 outpatient clinic in a medical university hospital) between 1 January 1992 and 1 January 1998. At baseline, we excluded 10 patients who had a preexisting stroke, coronary artery disease, chronic heart failure, cardiac arrhythmia, (including atrial fibrillation), peripheral vascular disease, or obvious comorbidity (i.e., malignancy or infection). As a result, 811 patients were included in the JMS-ABPM Wave 1 Study, of whom 810 patients were successfully followed up (follow-up rate: 98%).

In the present study, we included 514 patients who underwent an ABPM, ECG, and blood sampling at baseline. As shown in Table 2, the included patients (n = 514) showed no significant differences in age (72.2 vs. 72.4 years), a proportion of men (37% vs. 41%) and current smoker (22% vs. 18%), 24-hour BP (138/78 vs. 138/78 mmHg), and antihypertensive medication use at follow-up time (57% vs. 46%) compared to those not included in the present study (n=297). The body mass index (BMI) was higher in the included patients compared to those not included (24.2 vs. 23.5 kg/m^2, $P = 0.01$).

Office BP was measured at the right arm with the patient in a sitting position after he or she had rested for at least 5 minutes. Office BP was calculated as the average of two measures on two separate occasions. Diabetes mellitus was defined as a fasting glucose level ≥ 126 mg/dl, a random nonfasting glucose level ≥ 200 mg/dl, hemoglobin A1c ≥ 6.2%, or the use of antihyperglycemic medication.

Table 2. Demographic and clinical characteristics between patients included and not included in the present study.

Parameter	Not Included n = 297	Included n = 514	*P*
Patients characteristics			
Age, years	72.4±11.5	72.2±8.7	0.84
Male, %	40.5	37.2	0.90
Body mass index, kg/m^2	23.5±3.5	24.2±3.6	0.01
Current smoker, %	18.2	21.8	1.45
Hyperlipidemia, %	12.8	21.8	9.97
Diabetes, %	8.4	14.4	6.20
eGFR, ml/min/1.73m^2	56.2±21.0	56.6±18.8	0.80
BP measurements			
Office SBP, mmHg	163±16	165±19	0.40
Office DBP, mmHg	89±14	91±14	0.17
Office PR, bpm	77±12	76±12	0.60
24-hours SBP, mmHg	138±16	138±17	0.52
24-hours DBP, mmHg	78±9	78±10	0.23
24-hours PR, bpm	71±7	71±7	0.67
Daytime SBP, mmHg	144±17	146±18	0.12
Daytime DBP, mmHg	81±10	82±11	0.14
Daytime PR, bpm	77±9	76±8	0.48
Nighttime SBP, mmHg	127±18	127±18	0.72
Nighttime DBP, mmHg	72±10	72±11	0.92
Nighttime PR, bpm	61±8	61±8	0.25
Nocturnal SBP dipping, %	-11±9	-12±8	0.14
Dipping status			
Extreme dipper, %	15.3	17.8	5.57
Dipper, %	35.8	42.5	
Non-dipper, %	34.9	30.6	
Reverse dipper, %	14.0	9.2	
Use of antihypertensive drugs at the follow-up time, %	46	57	10.0
CCB, %	26	43	0.31
ACE inhibitors, %	22	21	0.35
Diuretic	2	3	2.22
α blockers, %	1	1	0.80
β blockers, %	2	1	0.38
Laboratory data			
Fasting glucose*, mg/dl	89.0 (80.0-102.0)	89.0 (80.0-102.0)	0.70
Total cholesterol, mg/dl	196.8±36.0	201.6±33.9	0.59
Triglycerides*, mg/dl	124.0 (87.0-175.0)	127.0 (87.0-179.0)	0.13
High density lipoprotein*, mg/dl	45.0 (39.0-54.0)	45.7 (39.0-53.0)	0.88

Data are means ± SD or percentage, and *P* values were obtained by unpaired *t*-test or chi-squared test. Variables with skewed distributions (asterisk) are expressed as median (interquartile range), and *P* values were obtained by Mann-Whitney *U*-test. Significance was defined as $P < 0.05$. eGFR was calculated by the modification of diet in renal disease study equation modified for Japanese, using the following equation: eGFR (ml/min/1.73m^2)=194xage(years)$^{-0.287}$xserum creatinine (mg/dl)$^{-1.094}$ (for women, x0.739). Abbreviations: LVH, left ventricular hypertrophy; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate; ACE, angiotensin converting enzyme; CCB, calcium channel blocker.

The study protocol was approved by the Research Ethics Committee of the Department of Cardiovascular Medicine, Jichi Medical School, Japan, in 1998. All participants signed informed consent forms to participate in this study.

3.2. 24-hour ABPM

All hypertensive patients performed noninvasive 24-hour ABPM at 30-minute intervals on a weekday. Patients who were prescribe antihypertensive medications (n = 285) stopped them for at least 14 days before performing ABPM. Nocturnal BP was defined as the average BP measured from the time when patients went to bed until the time they got out of bed, and awake BP was defined as the average BP measured over the rest of the day. Nocturnal BP dipping was calculated as 100 x (1-nocturnal systolic BP (SBP)/awake SBP).[49]

We divided the patients into 4 groups according to the extent of nocturnal BP dipping as follows: extreme dippers, for whom the nocturnal SBP fall was ≥20%; dippers, for whom the fall was ≥10% but <20%; nondippers, for whom the fall was ≥0% but <10%; and reverse dippers, for whom the fall was <0%.

3.3. Measurement of neurohumoral and hemostatic factors

Blood samples were taken from cubital vein within two months after ABPM was conducted. Patients were instructed to fast overnight before the exam. Blood samples were obtained in the morning (8 AM – 10 AM) after 10 minutes in the supine position by the 2-syringe method into disposable siliconized vacuum glass tubes containing a 1/10 volume of 3.8% trisodium citrate for the measurement of hemostatic factors, and disodium EDTA for assaying neurohumoral factors. Serum epinephrine and norepinephrine levels were measured by high-pressure liquid chromatography (HLC-725CA Reagent Reactant D; Tosoh Co., Ltd., Tokyo,

Japan). The plasma fibrinogen level was determined using a 1-stage clotting assay kit (Dade Behring, Fort Lauderdale, FL). The plasma levels of F1+2 and PAI-1 antigen were determined using enzyme-immunosorbent assay kits for F1+2 (Behringwerke AG, Marburg, Germany) and PAI-1 (Biopool, Umea, Sweden). The plasma level of the vWF was measured using a specific ELISA kit (Shield Diagnostics, Ltd., Dundee, United Kingdom). This assay uses a monoclonal antibody against the functional epitope of vWF[52] rather than the polyclonal antibody, and the value for the commercially available pooled plasma (CTS standard plasma; Behringwerke AG) was taken as 100%. All measurements were conducted at a single commercial laboratory (SRL Inc., Tokyo, Japan) and the intra-assay and inter-assay coefficients of all tests were <7%.

3.4. Definition of ECG-LVH

ECG-LVH was defined as a high voltage of the QRS complex (R in V_5 + S in V_1 > 3.5 mV) with either a flat T wave (<10% of the R wave) or ST-segment depression and biphasic T waves.[53]

3.5. Follow-up and events

Each patient's medical records were reviewed after the patients were enrolled in the present study, and at that time we ascertained whether the patients were using antihypertensive medication or had had any incident CVD events (i.e., myocardial infarction or stroke). The follow-up assessments were performed over a 20-month period between 1996 and 1998, and the mean period of follow-up was 41 months (1-68 months).[48-51] When patients failed to come to the clinic, we interviewed them by telephone: none of them were diagnosed as having CVD events. Stroke events were diagnosed by the individual physicians who were caring for the patients at the time of the CVD events, and an independent neurologist reviewed the cases and confirmed

the diagnosis of stroke events. Stroke was defined as a sudden onset of neurological deficit persisted for ≥24 hours in the absence of any other disease process that could explain the symptom. Stroke included ischemic stroke (cerebral infarction and cerebral embolism), hemorrhagic stroke (cerebral hemorrhage and subarachnoid hemorrhage), and undefined type of stroke. Myocardial infarction was diagnosed based on the criteria of the WHO Multinational Monitoring of Trends and Determinants in the Cardiovascular Disease (MONICA) project.[54] Transient ischemic attack and angina were not included as outcomes.

3.6. Statistical analysis

All statistical analyses were performed with SPSS version 20.0 software (SPSS, Chicago, IL). Variables with normal distribution were expressed as means ± SD, and variables with skewed distribution were expressed as the median (interquartile range). The demographic variables and clinical characteristics in patients with and without ECG-LVH were compared using unpaired *t*-test. Categorical parameters were compared using chi-square test. Circulating levels of norepinephrine and hemostatic factors were compared using Mann-Whitney *U*-test. The cumulative incidence rate of CVD events among those with and without ECG-LVH was plotted as a Kaplan-Meier curve, and the difference was tested by the log-rank test. The hazard ratio (HR) and 95% confidence interval (95% CI) of CVD events for ECG-LVH were calculated using Cox regression analysis, including age, gender, smoking status, presence of diabetes mellitus, and the use of antihypertensive therapy at the time of final follow-up as adjusted factors. These adjusted factors were selected since they were significantly different between the hypertensive patients with and without ECG-LVH. We further included 24-hour or nocturnal SBP, circulating norepinephrine level, and plasma fibrinogen as adjusted factors. We assessed the interactions between ECG-LVH and BP parameters (i.e., high 24-hour BP, extreme dipping, and reverse

dipping) or neurohumoral and hemostatic factors in relation to CVD events. A two-sided $P < 0.05$ was defined as significant.

4. Results

The demographic variables and clinical characteristics according to the presence or absence of ECG-LVH at baseline are shown in Table 3. Patients with ECG-LVH (n = 106) were older and had a higher prevalence of men, current smoking, and diabetes mellitus compared with those without ECG-LVH. Office SBP and diastolic BP (DBP), 24-hour SBP and DBP, daytime SBP and DBP, and nighttime SBP and DBP were higher in patients with ECG-LVH than those without it (all $P < 0.001$).

Table 4 shows comparisons of the neurohumoral and hemostatic factors between patients with and without ECG-LVH. Patients with ECG-LVH showed higher levels of norepinephrine than those without ECG-LVH ($P < 0.001$), whereas there were no significant differences in plasma renin activity, and circulating levels of fibrinogen, F1+2, vWF, and PAI-1 between the two groups.

During follow-up (average of 41 months, range 1-68 months, 1,751 person-years), 43 stroke (ischemic 30, hemorrhagic 5, undefined 8) and 3 myocardial infarction occurred. The Kaplan-Meier curve (Figure 3) shows that those with ECG-LVH had a higher cumulative incidence rate of CVD events compared to those without ECG-LVH ($P < 0.001$ by log-rank test). The Cox regression analysis showed that the patients with ECG-LVH had a higher risk of CVD events, and the association remained significant after adjustment for age, gender, smoking status, presence of diabetes mellitus, and the use of antihypertensive drugs at the time of follow-up (model 1 in Table 5). Further adjustment for high 24-hour BP (≥130/80 mmHg, model 2a), day

Table 3. Baseline characteristics of the study population according to the presence or absence of ECG-LVH

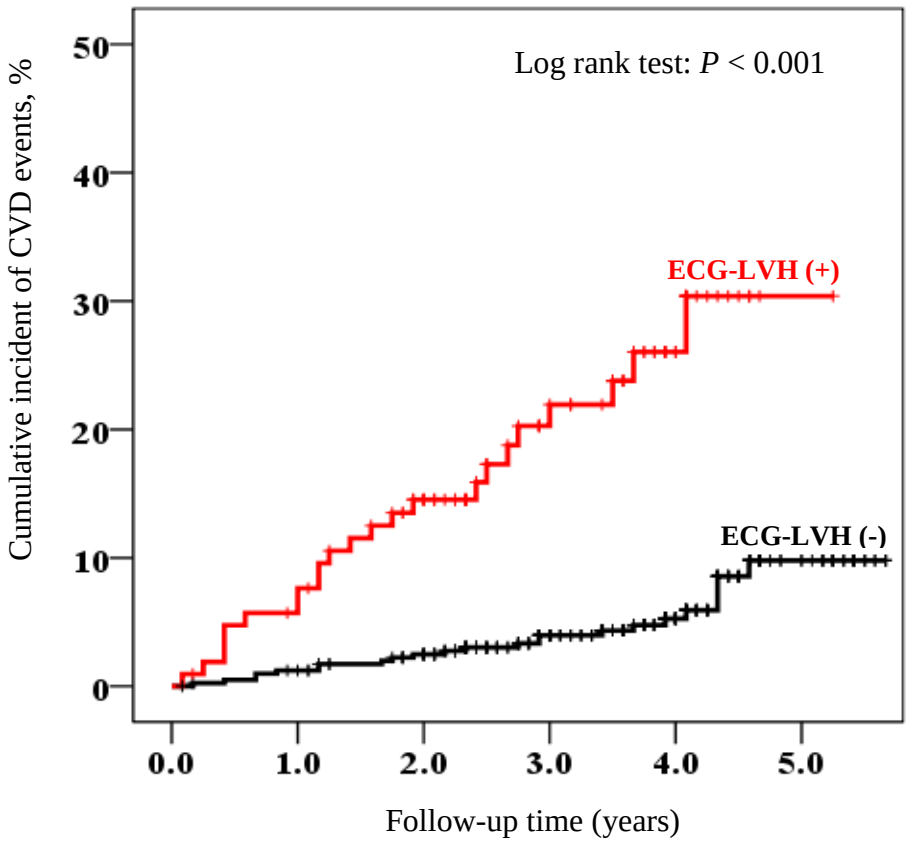
Parameter	ECG-LVH(-) n = 408	ECG-LVH(+) n = 106	*P*
Patients characteristics			
Age, years	71.8±8.7	73.9±8.5	0.03
Male, %	32.6	54.7	<0.001
Body mass index, kg/m^2	24.3±3.6	23.6±3.3	0.08
Current smoker, %	18.9	34.9	0.001
Hyperlipidemia, %	22.3	19.8	0.60
Diabetes, %	12.5	21.7	0.02
eGFR, ml/min/1.73m^2	56.4±13.4	54.3±13.1	0.15
BP measurements			
Office SBP, mmHg	162±17	174±23	<0.001
Office DBP, mmHg	90±14	96±16	<0.001
Office PR, bpm	77±12	75±12	0.05
24-hour SBP, mmHg	136±15	149±17	<0.001
24-hour DBP, mmHg	77±9	84±11	<0.001
24-hour PR, bpm	71±7	70±8	0.14
Daytime SBP, mmHg	143±17	155±19	<0.001
Daytime DBP, mmHg	81±10	87±11	<0.001
Daytime PR, bpm	77±8	75±8	0.07
Nocturnal SBP, mmHg	124±16	137±22	<0.001
Nocturnal DBP, mmHg	71±10	78±13	<0.001
Nocturnal PR, bpm	71±10	78±13	0.75
Nocturnal SBP dipping, %	-13±9	-11±9	0.045
Dipping status			
Extreme dipper, %	22.5	17.9	0.24
Dipper, %	46.3	40.6	
Non-dipper, %	31.1	41.5	
Reverse dipper, %	7.8	10.4	
Use of antihypertensive drugs at the follow-up time, %	54	68	0.01
CCB, %	38	43	0.31
ACE inhibitors, %	19	32	0.003
Diuretics, %	4	6	0.41
α blockers, %	2	0	0.22
β blockers, %	1	1	1.00
Laboratory data			
Fasting glucose*, mg/dl	89.0 (80.0-102.0)	90.0 (81.8-109.3)	0.38
Total cholesterol, mg/dl	201.6±33.8	201.7±34.5	0.97
Triglycerides*, mg/dl	127.5 (87.0-179.0)	136.0 (90.5-175.0)	0.58
High density lipoprotein*, mg/dl	45.0 (38.0-53.0)	46.5 (40.0-54.0)	1.72

Data are means ± SD or percentage, and *P* values were obtained by an unpaired *t*-test or chi-square test. Variables with skewed distributions (asterisk) are expressed as median (interquartile range), and *P* values were obtained by Mann-Whitney *U*-test. Significance was defined as $P < 0.05$. eGFR was calculated by the modification of diet in renal disease study equation modified for Japanese, using the following equation: eGFR (ml/min/1.73m^2)=194xage(years)$^{-0.287}$xserum creatinine (mg/dl)$^{-1.094}$ (for women, x0.739). Abbreviations: ACE, angiotensin converting enzyme; CCB, calcium channel blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LVH, left ventricular hypertrophy; PR, pulse rate; SBP, systolic blood pressure.

Table 4. Neurohumoral and hemostatic factors of the study population according to the presence or absence of ECG-LVH

Variable	**ECG-LVH(-) n = 408**	**ECG-LVH(+) n = 106**	***P***
Neurohumoral factors			
Plasma renin activity, ng/ml/hr	0.5 (0.2-1.00)	0.4 (0.2-0.9)	0.32
Epinephrine, pg/ml	34.0 (22.0-53.0)	42.0 (22.5-64.0)	0.11
Norepinephrine, pg/ml	335.0 (234.3-506.3)	435.0 (287.5-629.8)	<0.001
Hemostatic factors			
Fibrinogen, mg/dl	262.0 (230.0-296.0)	277.5 (230.5-330.3)	0.08
Prothrombin fragment 1+2, nmol/L	1.42 (1.14-1.71)	1.39 (1.13-1.90)	0.98
von Willebrand factor, %	158.4 (132.0-198.0)	161.0 (133.6-200.5)	0.39
Plasminogen activator inhibitor-1, ng/ml	34.1 (24.4-56.4)	39.0 (24.1-67.2)	0.68

Variables are skewed distribution, thus data are expressed as median (interquartile range). *P* values were obtained by Mann-Whitney *U*-test. Significance was defined as $P < 0.05$. Abbreviations: ECG, electrocardiography; LVH, left ventricular hypertrophy.



Number at risk					
ECG-LVH	(+)	408	400	292	40
	(-)	106	98	48	1

Figure 3. Kaplan-Meier curve for cumulative incidence rate of CVD events in hypertensive patients with LVH and without LVH. Abbreviations: CVD, cardiovascular disease; ECG, electrocardiography; LVH, left ventricular hypertrophy.

Table 5. Cox regression analysis for CVD events in older hypertensive patients (n=514)

Variable	HR	95% CI	*P*	*P* for Interaction
Model 1				
ECG-LVH	4.42	2.37-8.22	0.0001	
Model 2a				
ECG-LVH	3.58	1.93-6.67	0.0001	
High 24-hour BP (≥130/80 mmHg)	4.33	1.65-11.33	0.003	
Model 2b				
ECG-LVH × high 24-hour BP	0.53	0.10-3.67		0.52
Model 3				
ECG-LVH	3.33	1.70-6.54	0.0001	
24-hour SBP + 10 mmHg	1.35	1.05-1.74	0.018	
Model 4				
ECG-LVH	3.58	1.88-6.80	0.0001	
Daytime SBP + 10 mmHg	1.34	1.07-1.68	0.01	
Model 5				
ECG-LVH	3.64	1.88-7.07	0.0001	
Nocturnal SBP + 10 mmHg	1.22	1.00-1.53	0.048	
Model 6a				
ECG-LVH	3.95	2.05-7.62	0.0001	
Nocturnal SBP dipping status				
Extreme dipping	3.15	1.37-7.24	0.007	
Dipping		1 (reference)		
Non-dipping	2.06	0.96-4.43	0.063	
Reverse dipping	2.81	1.09-7.25	0.032	
Model 6b				
ECG-LVH × extreme dipping	1.78	0.42-7.58		0.43
Model 6c				
ECG-LVH × reverse dipping	0.79	0.15-4.13		0.78

Hazard ratios (HR) and 95% confidence interval (CI) of each BP indices are shown. Each model was adjusted by age, gender, smoking status, presence of diabetes mellitus, and the use of antihypertensive drugs at follow-up time. To assess the interaction between ECG-LVH and BP parameters in relation to CVD events, model 2b included ECG-LVH, high 24-hour BP, and ECG-LVH × high 24-hour BP, model 6b included ECG-LVH, extreme dipping, and ECG-LVH × extreme dipping, and model 6c included ECG-LVH, reverse dipping, and ECG-LVH × reverse dipping in the same models. Significance was defined as $P < 0.05$. Abbreviations: BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; SBP, systolic blood pressure.

Table 6. Cox regression analysis for CVD events in older hypertensive patients (n=514)

Variable	HR	95% CI	*P*	*P* for Interaction
Model 1				
ECG-LVH	3.58	1.93-6.67	0.0001	
Model 2a				
ECG-LVH	4.03	2.16-7.53	0.0001	
Serum norepinephrine + 10 pg/ml	1.002	1.0004-1.003	0.01	
Model 2b				
ECG-LVH × serum norepinephrine	1.00	0.99-1.00		0.95
Model 3				
ECG-LVH	4.29	2.29-8.04	0.0001	
Fibrinogen + 10 mg/dl	1.00	0.99-1.00	0.26	

Hazard ratios (HRs) and 95% confidence interval (CI) of neurohumoral and hemostatic factor. Each model was adjusted by age, gender, smoking status, presence of diabetes mellitus, the use of antihypertensive drugs at follow-up time and high 24-hour BP. To assess the interaction between ECG-LVH and norepinephrine levels in relation to CVD events, model 2b included ECG-LVH, serum norepinephrine levels, and ECG-LVH × serum norepinephrine levels in the same models. Significance was defined as $P < 0.05$. Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; LVH, left ventricular hypertrophy.

time SBP (model 4), nighttime SBP (model 5), and nocturnal SBP dipping (model 6a) did not change the results. A significant interaction of ECG-LVH with high 24-hour BP (model 2b in Table 5), extreme dipping (model 6b), or reverse dipping (model 6c) was not observed. We also analyzed the interaction between ECG-LVH and daytime SBP on CVD risk, and the results were null (HR, 1.15; 95% CI, 0.85-1.55, $P = 0.35$).

The association between ECG-LVH and CVD events was independent of circulating levels of norepinephrine (model 2a in Table 6) and fibrinogen (model 3). Higher norepinephrine levels were associated with a higher risk for CVD events independently of ECG-LVH. The interactions of ECG-LVH with norepinephrine (model 2b in Table 6) in relation to CVD events were not significant. When we entered the 4 variables (ECG-LVH, high 24-hour BP, and norepinephrine and fibrinogen levels) together in the same model, the CVD risks of ECG-LVH (HR, 4.43; 95% CI, 2.38-8.25) and high 24-hour BP (HR, 4.39; 95% CI 1.67-11.50) were significant, but the corresponding values of higher norepinephrine (HR, 1.71; 95% CI, 0.91-3.19) and fibrinogen (HR, 1.00; 95% CI, 0.99-1.00) were not significant.

5. Discussion

The present prospective study with older hypertensive patients (mean age 72.3 years and mean follow-up of 41 months) demonstrate that ECG-LVH was associated with a higher risk for CVD events, independent of higher 24-hour BP, nocturnal SBP, and higher circulating levels of fibrinogen and norepinephrine. Each of high 24-hour BP, higher nocturnal SBP, and higher circulating norepinephrine levels was associated with a higher risk for CVD events, independent of the presence of ECG-LVH. There were no significant interactions of ECG-LVH with high 24-

hour BP, higher nocturnal SBP, or higher circulating norepinephrine levels in relation to CVD events.

Desai *et al.*[55] suggested that among 15,792 participants free from clinical CVD at baseline (mean age 54.7 years; 45% men; median follow-up of 11.2 years), ECG-LVH was associated with a higher risk of incident CVD events (i.e., coronary heart disease/nonfatal myocardial infarction, heart failure, stroke, and CVD death) in men (HR, 1.36; 95% CI, 1.10-1.68) and women (HR, 1.43; 95% CI, 1.17-1.94). Office SBP was used as adjusted factors.

Okin *et al.*[42] suggested that among 8,854 hypertensive patients (mean age 67±7 years; 46% men; mean follow-up of 4.8 years), an LV strain pattern on ECG was associated with a higher risk for CVD mortality (HR, 1.53; 95% CI, 1.2-2.0), independent of conventional cardiovascular risk factors including office BP. Jissho *et al.*[56] demonstrated that among 3,230 Japanese elderly (mean age 73.5 years; 43% men; mean follow-up of 2 years), ECG-LVH was a significant predictor of CVD events (particularly cerebrovascular disease) independent of office SBP. None of these studies adjusted for 24-hour BP. Our findings complement and extend the prior evidence[57-59] by showing that the association between ECG-LVH and the risk of CVD events was independent of high 24-hour BP and higher nocturnal SBP.

Schlaich *et al.*[23] suggested that among 26 hypertensive patients (mean age 43 years; 75% men), those with echocardiographic LVH had a higher SNA, assessed by muscle SNA, compared to those without LVH. We found that the hypertensive patients with ECG-LVH had higher circulatory norepinephrine levels compared to those without ECG-LVH. Circulatory catecholamine levels are influenced not only by catecholamine production but also by tissue clearance as well as the process of reuptake of catecholamine to neurons, which could attenuate

the implications of circulating catecholamine levels as a marker of SNA.[60,61] Our data suggest that the CVD risk of ECG-LVH was independent of circulating catecholamine levels, but further researches using more precise assessment of SNA are warranted.

Lip *et al.*[33] suggested that among 178 hypertensive patients (86 men, mean age 54±15 years), those with echocardiographic LVH had higher levels of circulating fibrinogen levels compared with those without LVH. We observed that circulating levels of fibrinogen, F1+2, vWF, and PAI-1 were not significantly different between those with and without ECG-LVH. The reasons for the discrepant result remain uncertain, but racial differences in the circulating levels of hemostatic factors and their impact on CVD events may exist.[62,63]

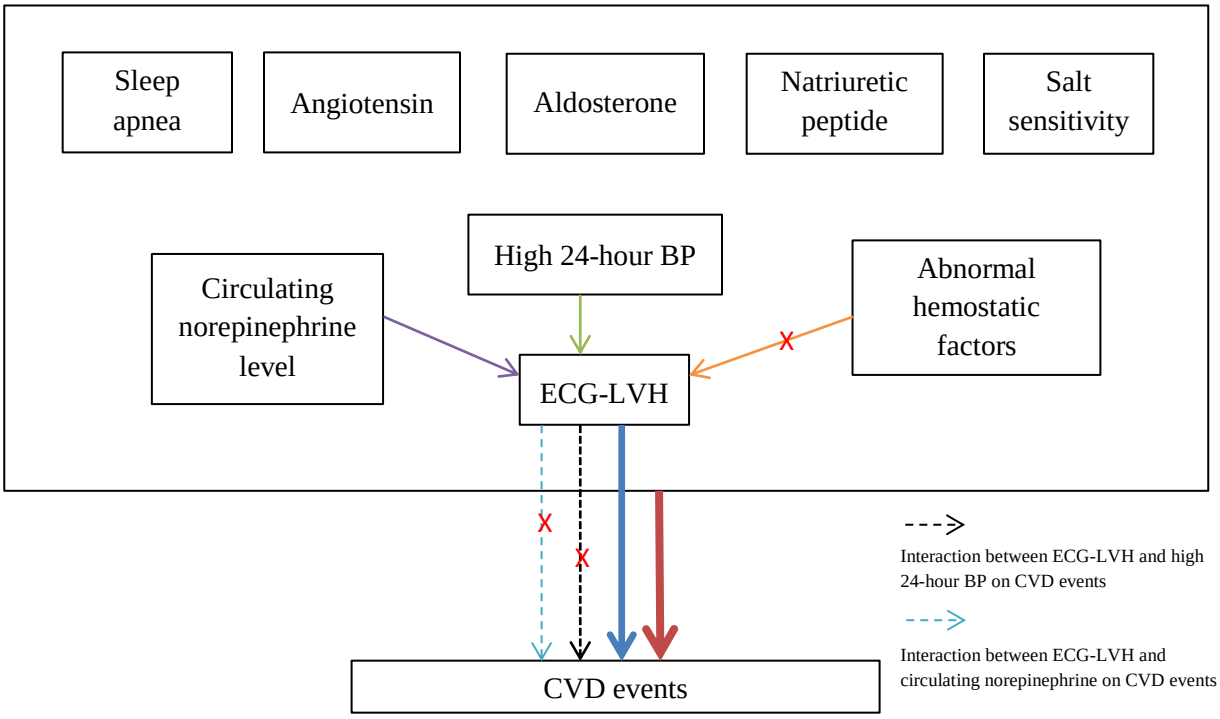


Figure 4. Schematic draw illustrating the association between cardiovascular risk factors and CVD events. Abbreviations: BP, blood pressure; CVD, cardiovascular disease; ECG, electrocardiography; LVH, left ventricular hypertrophy; SNA, sympathetic nerve activity.

In the present study, the association between ECG-LVH and CVD events could not be explained by high 24-hour SBP, higher nocturnal SBP, and higher circulating levels of norepinephrine and hemostatic factors. Other potential mechanisms unmeasured in the present study include sleep apnea,[64] neurohumoral factors (e.g., circulating levels of angiotensin, aldosterone, and natriuretic peptide),[65,66] and salt sensitivity.[67] These factors have been shown to share common etiology of LVH and CVD events, and thus further investigations are required to determine whether the association between ECG-LVH and CVD events observed in the present study is independent of these uncontrolled factors (Figure 4).[64-70]

There are several limitations in the present study. First, the number of CVD events was small, so we could not separate CVD events into stroke (or its subtypes) and myocardial infarction. Second, some patients received antihypertensive medication during follow-up, which could have led to underestimate true association between ECG-LVH and CVD events. Third, during the follow-up, 49 patients died; among them, 29 patients died from non-myocardial infarction or nonstroke, which may compete as outcomes. In other words, individuals may not experience myocardial infarction or stroke events for which they are destined if death occurs first. Fourth, we did not assess how many patients declined our offer to participate in the present study, suggesting the possibility of a selection bias. Lastly, our study patients were recruited from outpatients at clinics or hospitals in selected areas, so that our results may not be generalized to other race/ethnic populations or even other Japanese hypertensive elderly individuals.

6. Conclusions

Among older hypertensive patients, those with ECG-LVH had higher 24-hour and nocturnal SBP, and higher circulating norepinephrine levels compared to those without ECG-

LVH. ECG-LVH was associated with a higher risk for CVD events, and the association was independent of higher 24-hour BP, nocturnal SBP, and circulating norepinephrine levels and other risk factors.

Acknowledgments

I express my sincere gratitude to Prof. Kazuomi Kario for the enlightening discussions, kind support and continual encouragement. His enthusiasm and expertise in cardiovascular medicine, especially in the field of hypertension, contributed greatly to the motivation and direction of my interest in clinical research. I sincerely thank Assoc. Prof. Satoshi Hoshide and Yuichiro Yano for their valuable discussions, thoughtful support and advices. I thank Tomokazu Ikemoto, Michiaki Nagai, Joji Ishikawa, Toshinobu Saito, Assoc. Professors Kazuo Eguchi, Takaaki Katsuki, Nobuhiko Ogata, Yasushi Imai, Masahisa Shimpo, and all of the staff of the Department of Internal Medicine, Division of Cardiovascular Medicine, Jichi Medical University for their kind collaboration and discussions. Their valuable advice supported me during my PhD study in Japan.

I also sincerely thank Professors Shinichiro Koyama, Naoyuki Taga, and Hiroshi Miyashita for their valuable suggestions and constructive comments during the preparation of this dissertation, and Prof. Takashi Yashiro and Prof. Toshiko Yada for their kind advice, encouragement and supports during my PhD study at Jichi Medical University.

I learned so much from both academic and non-academic activities during my long stay in Japan, especially in Shimotsuke City, Tochigi Prefecture. Many thanks are due to all my colleagues including Japanese and Indonesian students who have helped me many times.

I also thank the Directorate General of Higher Education of the Ministry of National Education, Indonesia for their financial support through Beasiswa Unggulan, and I appreciate the

funds that I received as a research assistant at the Department of Cardiovascular Medicine, Jichi Medical University and the scholarship from the Hashiya Scholarship Foundation.

Last but not least, I would like to express my special thanks and gratitude to my father (Prof. Edison Munaf), my mother (Prof. Rahmiana Zein), my wife (Medina Dwitia Sari), my son (Bagas Naokiromena Eijiro), my older brother (Rizki Edmi Edison), and my younger brother (Ebil Fuji Edison) for their patience, advice, and support. Special thanks are extended to my parents-in-law. They are a great source of mental strength and enjoyment for me and have made my work worthwhile even in the most difficult times.

Reference

1. Kannel WB, Dawber TR, Kagan A, Revorskie N, Stokes J III. Factors of risk in the development of coronary heart disease-six year follow-up experience. *Ann Intern Med* 55:33-50, 1961.
2. Redondo FJ, Berges DF, Calderon A, Sanchez LC, Lozano L, Barrios V. Prevalence of left-ventricular hypertrophy by multiple electrocardiographic criteria in general population: Hermex study. *J Hypertens* 30:1460-1467, 2012.
3. Gosse P. Left ventricular hypertrophy as a predictor of cardiovascular risk. *J Hypertens* 23(suppl 1):S27-S33, 2005.
4. Levy D, Salomon M, D'Agostino RB, Belanger AJ, Kannel WB. Prognostic implications of baseline electrocardiographic features and their serial changes in subjects with left ventricular hypertrophy. *Circulation* 90:1786-1793, 1994.
5. Fagard RH, Staessen JA, Thijs L, Celis H, Birkenhäger WH, Bulpitt CJ, de Leeuw PW, Leonetti G, Sarti C, Tuomilehto J, Webster J, Yodfat Y. Prognostic significance of electrocardiographic voltages and their serial changes in elderly with systolic hypertension. *Hypertension* 44:459-464, 2004.
6. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart study. *N Engl J Med* 322:1561-1566, 1990.
7. Morisco C, Sadoshima J, Trimarco B, Arora R, Vatner DE, Vatner SF. Is treating cardiac hypertrophy salutary or detrimental: the two faces of Janus. *Am J Physiol Heart Circ Physiol* 284:H1043-H1047, 2003.
8. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling-concepts and clinical implications: A consensus paper from an international forum on cardiac remodeling. *J Am Coll Cardiol* 35:569-582, 2000.
9. Tallarida RJ, Rusy BF, Loughnane MH. Left ventricular wall acceleration and the law of Laplace. *Cardiovasc Res* 4:217-223, 1970.
10. Hill JA, Olson EN. Cardiac plasticity. *N Engl J Med* 358:1370-1380, 2008.

11. Ganau A, Devereux RB, Roman MJ, de Simone G, Pickering TG, Saba PS, Vargiu P, Simongini I, Laragh JH. Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. *J Am Coll Cardiol* 19:1550-1558, 1992.
12. Schwartzkopff B, Frenzel H, Dieckerhoff J, Betz P, Flasshove M, Schulte HD, Mundhenke M, Motz W, Strauer BE. Morphometric investigation of human myocardium in arterial hypertension and valvular aortic stenosis. *Eur Heart J* 13(suppl D):17-23, 1992.
13. Hammond IW, Devereux RB, Alderman MH, Lutas EM, Spitzer MC, Crowley JS, Laragh JH. The prevalence and correlates of echocardiographic left ventricular hypertrophy among employed patients with uncomplicated hypertension. *J Am Coll Cardiol* 7:639-650, 1986.
14. Mancia G, Omboni S, Parati G. The importance of blood pressure variability in hypertension. *Blood Press Monit* 5 Suppl 1:S9-S15, 2005.
15. Narkiewicz K, Winnicki M, Schroeder K, Phillips BG, Kato M, Cwalina E, Somers VK. Relationship between muscle sympathetic nerve activity and diurnal blood pressure profile. *Hypertension* 39:168-172, 2002.
16. Mancia G, Parati G. Ambulatory blood pressure monitoring and organ damage. *Hypertension* 36:894-900, 2000.
17. Mancia G, Zanchetti A, Agabiti-Rosei E, Benemio G, De Cesaris R, Fogari R, Pessina A, Porcellati C, Rappelli A, Salvetti A, Trimarco B. Ambulatory blood pressure is superior to clinic blood pressure in predicting treatment-induced regression of left ventricular hypertrophy. *Circulation* 95:1464-1470, 1997.
18. Verdecchia P, Schillacci G, Guerrieri M, Gatteschi C, Benemio G, Boldrini F, Porcellati C. Cicardian blood pressure changes and left ventricular hypertrophy in essential hypertension. *Circulation* 81:528-536, 1990.
19. Andrikou I, Tsioufis C, Thomopoulus C, Kasiakogias A, Dimitriadis K, Andrikou E, Aragiannis D, Syrseloudis D, Soulis D, Stefanadis C. Nighttime vs. daytime blood pressure as a predictor of changes in left ventricular mass in hypertensive subjects. *Hypertens Res* 36:967-971, 2013.
20. Kario K, Hoshide S, Shimizu M, Yano Y, Eguchi K, Ishikawa J, Ishikawa S, Shimada K. Effect of dosing of angiotensin II receptor blockade titrated by self-measured blood

pressure recordings on cardiorenal protection in hypertensives: the Japan Morning Surge-Target Organ Protection (J-TOP) study. *J Hypertens* 28:1547-1583, 2010.

21. Patel MB, Stewart JM, Loud AV, Anversa P, Wang J, FIegel L, Hintze TH. Altered function and structure of the heart in dogs with chronic elevation in plasma norepinephrine. *Circulation* 84:2091-2100, 1991.
22. Yamori Y, Tarazi RC, Ooshima A. Effect of beta-receptor-blocking agents on cardiovascular structural changes in spontaneous and noradrenaline-induced hypertension in rats. *Clin Sci* 59:457s-460s, 1980.
23. Grassi G, Cattaneo BM, Seravalle G, Lanfranchi A, Mancia G. Baroreflex control of sympathetic nerve activity in essential and secondary hypertension. *Hypertension* 31:68-72, 1998.
24. Greenwood JP, Scott EM, Stocker JB, Mary DA. Hypertensive left ventricular hypertrophy: relation to peripheral sympathetic drive. *J Am Coll Cardiol* 38:1711-1717, 2001.
25. Schlaich MP, Kaye DM, Lambert E, Sommerville M, Socratous F, Esler MD. Relation between cardiac sympathetic activity and hypertensive left ventricular hypertrophy. *Circulation* 108:560-565, 2003.
26. Strand AH, Gudmundsdottir H, Os I, Smith G, Westheim AS, Bjørnheim R, Kjeldsen E. Arterial plasma noradrenaline predicts left ventricular mass independently of blood pressure and body build in men who develop hypertension over 20 years. *J Hypertens* 42:905-913, 2006.
27. Mancia G. Björn Folkow Award Lecture: the sympathetic nervous system in hypertension. *J Hypertens* 15: 1553-1565, 1997.
28. Reims HM, Sevre K, Høieggen A, Fossum E, Eide I, Kjeldsen SE. Blood viscosity: effects on mental stress and relations to autonomic nervous system function and insulin sensitivity. *Blood Press* 14:159-169, 2005.
29. Koga M, Sasaguri M, Miura S, Tashiro E, Kinoshita A, Ideishi M, Arakawa K. Plasma renin activity could be useful predictor of left ventricular hypertrophy in essential hypertensives. *J Hum Hypertens* 12:455-461, 1998.

30. Malmqvist K, Öhman KP, Lind L, Nyström F, Kahan T. Relationships between left ventricular mass and the renin-angiotensin system, catecholamines, insulin, and leptin. *J Intern Med* 252:430-439, 2002.
31. Catena C, Colussi G, Valeri M, Sechi LA. Association of aldosterone with left ventricular mass in hypertension: interaction with plasma fibrinogen levels. *Am J Hypertens* 26:111-117, 2013.
32. Lip GY, Li-Saw-Hee FL. Does hypertension confer a hypercoagulable state? *J Hypertens* 16:913-916, 1998.
33. Lip GY, Blann AD, Jones AF, Lip PL, Beevers DG. Relation of endothelium, thrombogenesis, and hemorheology in systemic hypertension to ethnicity and left ventricular hypertrophy. *Am J Cardiol* 80:1566-1571, 1997.
34. Catena C, Colussi G, Fedrizzi S, Sechi LA. Association of a prothrombotic state with left-ventricular diastolic dysfunction in hypertension: a tissue-Doppler imaging study. *J Hypertens* 31:2077-2084, 2013.
35. Palmieri V, Celentano A, Roman MJ, de Simone G, Lewis MR, Best L, Lee ET, Robbins DC, Howard BV, Devereux RB. Fibrinogen and preclinical echocardiographic target organ damage. *Hypertension* 38:1068-1074, 2001.
36. Diamantopoulos EJ, Andreadis EA, Vassilopoulos CV, Theodorides TG, Giannakopoulos NS, Chatzis NA, Christopoulou-Kokkinou VD. Increased plasma plasminogen activator inhibitor-1 levels: possible marker of hypertensive organ damage. *Clin Exp Hypertens* 25:1-9, 2003.
37. Arentt DK, McClelland RL, Bank A, Bluemke DA, Cushman M, Szalai AJ, Jain N, Gomes AS, Heckbert SR, Hundley WG, Lima JA. Biomarkers of inflammation and hemostasis associated with left ventricular mass: the multiethnic study of atherosclerosis (MESA). *Int J Epidemiol Genet* 2:391-400, 2011.
38. Adderley SR, Fitzgerald DJ. Glycoprotein IIb/IIIa antagonists induce apoptosis in rat cardiomyocytes by caspase-3 activation. *J Biol Chem* 275:5760-5766, 2000.
39. Rosello-Lleti E, Rivera M, Martinez-Dolz L, Gonzalez Juanatey JR, Cortes R, Jordan A, Morillas P, Lauwers C, Calabuig JR, Antorenna I, de Rivas B, Portoles M, Bertomeu V. Inflammatory activation and left ventricular mass in essential hypertension. *Am J Hypertens* 22:444-450, 2009.

40. Lominadze D, Dean WL, Tyagi SC, Roberts AM. Mechanisms of fibrinogen-induced microvascular dysfunction during cardiovascular disease. *Acta Physiol* 198:1-13, 2010.
41. Alfakih K, Reid S, Hall A, Sivananthan MU. The assessment of left ventricular hypertrophy in hypertension. *J Hypertens* 24:1223-1230, 2006.
42. Okin PM, Devereux RB, Nieminen MS, Jern S, Oikarinen L, Viitasalo M, Toivonen L, Kjeldsen SE, Julius S, Snapinn S, Dahlöf B. Electrocardiographic strain pattern and prediction of cardiovascular morbidity and mortality in hypertensive patients. *Hypertension* 44:48-54, 2004.
43. Bang CN, Devereux RB, Okin PM. Regression of electrocardiographic left ventricular hypertrophy or strain is associated with lower incidence of cardiovascular morbidity and mortality in hypertensive patients independent of blood pressure reduction – A LIFE review. *J Electrocardiol* 47:630-635, 2014.
44. Mathew J, Sleight P, Lonn E, Johnstone D, Pogue J, Yi Q, Bosch J, Sussex B, Probstfield J, Yusuf S. Reduction of cardiovascular risk by regression of electrocardiographic markers of left ventricular hypertrophy by the angiotensin-converting enzyme inhibitor Ramipril. *Circulation* 104:1615-1621, 2001.
45. Cuspidi C, Grassi G. Electrocardiographic diagnosis of left-ventricular hypertrophy: good news for the clinician? *J Hypertens* 30:884-886, 2012.
46. Mancia G, Fagard R, Narkiewicsz K, Redan J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, de Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchof P, Kjeldsen SE, Laurent S, Manolis A, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F. 2013 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension(ESH) and the European Society of Cardiology (ESC): ESH/ESC Task Force for the Management of Arterial Hypertension. *J Hypertens* 10:1925-1938, 2013.
47. Shimamoto K, Ando K, Fujita T, Hasebe N, Higaki J, Horiuchi M, Imai Y, Imaizumi T, Ishimitsu T, Ito M, Ito S, Itoh H, Iwao H, Kai H, Kario K, on behalf of The Japanese Society of Hypertension Committee for Guideline for the Management of Hypertension. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014). *Hypertens Res* 37:253-392, 2014.

48. Kario K, Pickering TG, Umeda Y, Hoshide S, Hoshide Y, Morinari M, Murata M, Kuroda T, Schwartz JE, Shimada K. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. *Circulation* 107:1401-1406, 2003.
49. Kario K, Yano Y, Matsuo T, Hoshide S, Eguchi K, Shimada K. Additional impact of morning haemostatic risk factors and morning blood pressure surge on stroke risk in older Japanese hypertensive patients. *Eur Heart J* 32:574-580, 2011.
50. Ishikawa J, Tamura Y, Hoshide S, Eguchi K, Ishikawa S, Shimada K, Kario K. Low-grade inflammation is a risk factor for clinical stroke events in addition to silent cerebral infarcts in Japanese older hypertensives: the Jichi Medical School ABPM Study, wave 1. *Stroke* 38:911-917, 2007.
51. Yano Y, Hoshide S, Etoh T, Tamaki N, Yokota N, Kario K. Synergistic effect on chronic kidney disease and high circulatory norepinephrine level on stroke risk in Japanese hypertensive patients. *Atherosclerosis* 219:273-279, 2011.
52. Blaan AD, McCollum CN. von Willebrand factor and soluble thrombomodulin as predictors of adverse events among subjects with peripheral or coronary atherosclerosis. *Blood Coagul Fibrinolysis* 10:375-380, 1999.
53. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. *Am Heart J* 37:161-186, 1949.
54. The world health organization monica project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. WHO MONICA Project Principal Investigators. *J Clin Epidemiol* 41:105-114, 1988.
55. Desai CS, Ning H, Llyod-Jones DM. Competing cardiovascular outcomes associated with electrocardiographic left ventricular hypertrophy: the Atherosclerosis Risk in Communities Study. *Heart* 98:330-334, 2012.
56. Jissho S, Shimada K, Taguchi H, Yoshida K, Fukuda S, Tanaka H, Yoshikawa J, Yoshikawa 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* 74:938-945, 2010.

57. Pierdomenico SD, Lappena D, Cuccurullo F. Regression of echocardiographic left ventricular hypertrophy after 2 years of therapy reduces cardiovascular risk in patients with essential hypertension. *Am J Hypertens* 21:464-470, 2008.
58. Verdecchia P, Porcellati C, Reboldi G, Gattobigio R, Borgioni C, Pearson TA, Ambrosio G. Left ventricular hypertrophy as an independent predictor of acute cerebrovascular events in essential hypertension. *Circulation* 104:2039-2044, 2001.
59. Peterson GE, de Backer T, Contreras G, Wang X, Kendrick C, Greene T, Appel LJ, Randall OS, Lea J, Smogorzewski M, Vagaonescu T, Phillips RA. Relationship of left ventricular hypertrophy and diastolic function with cardiovascular and renal outcomes in African Americans with hypertensive chronic kidney disease. *Hypertension* 62:518-525, 2013.
60. Goldstein DS. Plasma catecholamines and essential hypertension. An analytical review. *Hypertension* 5:86-99, 1983.
61. Eisenhofer G, Esler MD, Meredith IT, Dart A, Cannon RO, Quyyumi AA, Lambert G, Chin J, Jennings GL, Goldstein DS. Sympathetic nervous function in human heart as assessed by cardiac spillovers of dihydroxyphenylglycol and norepinephrine. *Circulation* 85:1775-1785, 1992.
62. Lutsey PL, Crushman M, Steffen LM, Green D, Barr RG, Herrington D, Ouyang P, Folsom AR. Plasma hemostatic factors and endothelial markers in four racial/ethnic groups: the MESA study. *J Thromb Haemost* 4:2629-2635, 2006.
63. Lowe GD, Rumley A. Coagulation, fibrinolysis, and cardiovascular disease. *Fibrinolysis Proteol* 13:91-98, 1999.
64. Noda A, Okada T, Yasuma F, Nakashima N, Yokota M. Cardiac hypertrophy in obstructive sleep apnea syndrome. *Chest* 107:1538-1544, 1995.
65. Cowan BR, Young AA. Left ventricular hypertrophy and renin-angiotensin system blockade. *Curr Hypertens Rep* 11:167-172, 2009.
66. Uusima P, Tokola H, Ylitalo A, Vuolteenaho O, Ruskoaho H, Risteli J, Linnaluoto M, Peuhkurinen K. Plasma B-type natriuretic peptide reflects left ventricular hypertrophy and diastolic function in hypertension. *Int J Cardiol* 97:251-256, 2004.

67. Heimann JC, Drumons S, Alves AT, Barbato AJ, Dichtchekenian V, Marcondes M. Left ventricular hypertrophy is more marked in salt-sensitive than in salt-resistant hypertensive patients. *J Cardiovasc Pharmacol* 17(Suppl 2):S122-S124, 1991.
68. Garcia MA, Rodriguez FC, Serra PC, Cataluna J, Gonzales CA, Moron I, Cantolla JD, Montserrat JM. Cardiovascular mortality in obstructive sleep apnea in the elderly: role of long term continuous positive airway pressure treatment: a prospective observational study. *Am J Respir Crit Care Med* 186:909-916, 2012.
69. Wang TJ, Larson MG, Levy D, Benjamin E, Leip EP, Omland T, Wolf PA, Vasan RS. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med* 350:655-663, 2004.
70. Strazullo P, D'Elia L, Kandala NB, Cappucio FP. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. *BMJ* 339:b4567, 2009.