Original Article

High-Density Lipoprotein Cholesterol and Insulin Resistance Are Independent and Additive Markers of Left Ventricular Hypertrophy in Essential Hypertension

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We examined whether plasma high-density lipoprotein-cholesterol (HDL-C) levels and glucose metabolism parameters are independent or additive predictors of left ventricular hypertrophy (LVH) in patients with untreated essential hypertension. The study group consisted of 41 Japanese patients with untreated essential hypertension and LVH (left ventricular mass index [LVMI] >125 g/m^2; age 58±6 years, mean±SD), and the control group consisted of 39 age-matched patients with untreated essential hypertension without LVH (LVMI ≤125 g/m^2; age 58±7 years). The following metabolic parameters were higher in the group with LVH: fasting plasma glucose (FPG) ($p<0.01$), fasting insulin concentration (F-IRI) ($p<0.0001$), and homeostasis model assessment (HOMA)-index ($p<0.0001$). Among the laboratory parameters investigated, plasma HDL-C levels were lower ($p<0.0001$), and triglyceride and uric acid levels were higher in the group with LVH ($p<0.05$ for both). The nighttime systolic and diastolic ambulatory blood pressure (ABP) ($p<0.0001$, $p<0.01$, respectively) and nighttime heart rate ($p<0.01$) were higher in patients with LVH. Multivariate logistic analysis identified HDL-C (odds ratio [OR]=0.92, 95% confidence interval [CI]=0.87–0.98, $p<0.05$), HOMA-index (OR=3.83, 95% CI=1.28–11.5, $p<0.05$) and nighttime systolic ambulatory blood pressure (ABP) (OR=1.06, 95% CI=1.00–1.13, $p<0.05$) as independent significant risk factors for LVH. Our findings suggest that HDL-C, HOMA-index and nighttime systolic ABP are independent predictors for the presence of LVH in Japanese patients with essential hypertension. (*Hypertens Res* 2007; 30: 125–131)

***Key Words*: insulin resistance, high-density lipoprotein cholesterol, left ventricular hypertrophy, essential hypertension**

Introduction

Left ventricular hypertrophy (LVH) is associated with high mortality (*1*), and patients with LVH frequently suffer from coronary artery disease, heart failure, stroke, and other cardiovascular complications (*2*). Despite growing awareness of the need to clinically identify LVH for cardiovascular risk stratification, the pathophysiological basis of left ventricular (LV) structural and functional abnormalities in patients with essential hypertension remains unclear.

It has been proposed that insulin resistance with compensatory hyperinsulinemia may be related to the pathogenesis of metabolic syndrome in essential hypertension (*3*), and there is

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an inverse relationship between insulin sensitivity and LV wall thickness in subjects with essential hypertension (*4*).

There is a normal decrease in blood pressure (BP) at night during rest, but some patients, referred to as non-dippers, do not exhibit this normal response when 24-h ambulatory blood pressure (ABP) is monitored. These patients are at increased risk of hypertension-associated end-organ damage of the brain, heart, and kidneys as well as poor prognosis for cardiovascular events compared to dipper patients whose nocturnal BP is reduced (*5*–*7*). Among patients with essential hypertension, non-dippers with increased insulin resistance have an increased risk for the development of LVH (*8*).

High-density lipoprotein cholesterol (HDL-C) levels are inversely related to the risk of cardiovascular events, and, recently, a negative relationship has been seen between HDL-C levels and left ventricular mass index (LVMI) (*9*–*11*). Additionally, low HDL-C levels are closely correlated with increased insulin resistance (*12*, *13*). However, although the relation of LVH to each of these potential hemodynamic and non-hemodynamic determinants has been reported, the multiple interrelations among HDL-C, insulin resistance, nocturnal ABP and the development of LVH in patients with essential hypertension have not been adequately investigated.

The present study was designed to test the hypothesis that LVH is independently associated with HDL-C, insulin resistance and nocturnal ABP in patients with newly diagnosed, untreated essential hypertension. We compared 24-h ABP, echocardiographic findings, and metabolic profiles of Japanese patients with untreated essential hypertension with and without LVH. These factors were then evaluated as independent predictors of LVH.

Methods

We screened 205 subjects (108 men, 97 women) who visited the outpatient clinic of Oita Red Cross Hospital during January 2002 and April 2006 because of abnormally high BP detected on medical examination. Among them, 80 patients (age: 58±7 years, mean±SD; 41 men and 39 women) fulfilled the following inclusion criteria and were enrolled in the present study. 1) The presence of essential hypertension defined as a mean 24-h systolic ambulatory blood pressure (sABP) greater than 135 mmHg or a mean 24-h diastolic ambulatory blood pressure (dABP) greater than 85 mmHg (*14*). 2) No treatment with antihypertensive medication prior to enrollment in this study. 3) Organic heart disease as determined by a treadmill exercise ECG. 4) No organic heart disease except for LVH. All participants in the LVH group met the criterion of LVH as assessed by echocardiography (see below). 5) No chronic disease such as renal failure, pulmonary disease, liver dysfunction, arteriosclerotic obliterans, or history of symptomatic cerebrovascular disease. 6) No treatment with antihypertensive agents, HMG Co-A reductase inhibitors, antidiabetic drugs or insulin. One hundred twenty-five of 205 patients were excluded from the study. Patients with secondary hypertension were excluded diagnosed by physical examination, chest X-ray, 12-lead ECG and echocardiography and biochemical examination. Forty-one of the 80 patients were diagnosed with LVH, and the other 39 patients were recruited as a group of age-matched hypertensives without LVH.

All subjects gave their written informed consent to participate in the study, and the study protocol was approved by the ethics committee of the Oita Red Cross Hospital.

Glucose and Lipid Measurements

Blood samples were obtained in the morning after an overnight (≥12 h) fast. Fasting blood glucose, fasting immunoreactive insulin (F-IRI), total cholesterol, triglycerides, HDL-C, hemoglobin A1c (HbA1c), uric acid and creatinine were determined using standard laboratory techniques. HDL-C was determined using standard laboratory measurements. HDL-C was categorized into two groups: low HDL-C (<40 mg/dl for men, <50 mg/dl for women), and high HDL-C (≥40 mg/dl for men, ≤50 mg/dl for women) (*15*).

Twenty-Four–Hour ABP Monitoring

During admission, the 24-h ABP was measured by the cuff-oscillometric method using an ABP monitoring system (TM-2425; A&D Co. Inc., Tokyo, Japan) with CO_2 gas–powered cuff inflation. The accuracy of this device has previously been validated (*16*). Blood pressure was measured every 30 min from 6:00 AM to 10:00 PM, and every 60 min from 10:00 PM to 6:00 AM on the following day (*17*). The mean BP value was computed for the awake period (between 6:00 AM and 10:00 PM) and the sleep period (between 10:00 PM and 6:00 AM) (*17*). The waking time, time of falling asleep, and quality of sleep were assessed by interview with each patient. Any patients who complained of sleep disturbance during ABP monitoring were excluded from the analysis. Subjects whose mean nighttime sABP fell by more than 10% compared to their mean day-time sABP value were defined as dippers. The remaining subjects were defined as non-dippers (*18*).

Echocardiography

M-mode 2-dimensional echocardiography and cardiac Doppler recordings were obtained by means of a phase-array echo-Doppler system. Echocardiograms were obtained in the standard manner using standard parasternal, short axis and apical views. The LV mass (g) was calculated by the method used in a previous study (*19*):

$$\text{LV mass} = 1.04\ \{(\text{LVIDd} + \text{IVSTd} + \text{PWTd})^3 - \text{LVIDd}^3\} - 14,$$

where LVIDd, left ventricular internal dimension at end-diastole; IVSTd, interventricular septal thickness at end-diastole; and PWTd, posterior wall thickness at end-diastole. The LV

Table 1. Clinical Characteristics

	LVH(–)	LVH(+)	*p* value
Age (years)	58±7	58±7	n.s.
Gender (men/women)	20/15	21/24	n.s.
BMI (kg/m^2)	24.7±1.8	25.4±2.0	n.s.
Smoking (%)	31	38	n.s.
24-h sABP (mmHg)	153±7	157±9	n.s.
24-h dABP (mmHg)	93±5	95±5	n.s.
24-h HR (beats/min)	68±5	70±5	n.s.
Daytime sABP (mmHg)	158±6	161±9	n.s.
Daytime dABP (mmHg)	96±5	98±5	n.s.
Daytime HR (beats/min)	71±5	73±5	n.s.
Nighttime sABP (mmHg)	136±9	147±10	<0.0001
Nighttime dABP (mmHg)	84±5	90±7	<0.0001
Nighttime HR (mmHg)	59±6	62±7	0.0404
Non-dippers (%)	31	64	0.0034
T-Chol (mg/dl)	218±38	207±33	n.s.
TGL (mg/dl)	152±35	165±42	0.0221
HDL-C (mg/dl)	50±12	39±10	<0.0001
FPG (mg/dl)	102±18	111±14	0.0144
F-IRI (μU/ml)	6.3±1.6	8.6±2.7	<0.0001
HOMA-index	1.6±0.6	2.4±0.8	<0.0001
HbA1c (%)	5.6±0.3	5.8±0.4	n.s.
Uric acid (mg/dl)	6.0±1.0	6.7±1.1	0.0062
Creatinine (mg/dl)	0.7±0.2	0.8±0.2	n.s.

Data are mean±SD. sABP, systolic ambulatory blood pressure; dABP, diastolic ambulatory blood pressure; HR, heart rate; BMI, body mass index; T-Chol, total cholesterol; TGL, triglyceride; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; F-IRI, fasting immunoreactive insulin; HOMA, homeostasis model assessment; HbA1c, hemoglobin A1c; n.s., not significant.

mass was divided by the body surface area to calculate the LVMI. Pulsed Doppler recordings were made from the standard apical 4-chamber view. The mitral inflow velocity was recorded with the sample volume at the mitral annulus level; the average of ≥3 cardiac cycles was taken. The following measurements were made: the peak velocity of early ventricular filling (*E*), the peak velocity of late ventricular filling (*A*), their ratio (*E*/*A*), and the deceleration time.

Definition of LVH

LVH was defined according to the previously established criterion (LVMI >125 g/m^2 for men and LVMI >110 g/m^2 for women) (*20*).

Insulin Resistance

Insulin resistance was evaluated by the homeostasis model assessment (HOMA)-index (*21*):

$$\text{HOMA-index} = (\text{fasting plasma insulin } [\mu U/ml] \times \text{fasting plasma glucose } [mmol/l])/22.5.$$

A HOMA-index greater than 2.5 indicates insulin resistance (*22*).

Statistical Analysis

All data are presented as the mean±SD. Statistical differences between mean values were assessed by *t*-test or ANOVA for analysis of continuous variables, and by non-parametric analysis using the Wilcoxon or Kruskal-Wallis test for variables that were not normally distributed.

Multiple logistic regression analysis was used to assess the combined influence of variables on LVH. Gender, smoking and non-dipping status were represented by dummy variables (1=male, 0=female; 1=presence, 0=absence) in logistic regression analysis. A model selection procedure was used to select the simplest regression model, that is, to determine significant risk factors. A value of $p<0.05$ was considered statistically significant.

Results

When patients were divided according to the presence or absence of LVH, there were no significant differences in age, gender, body mass index, or smoking rate between these groups (Table 1). Additionally, the 24-h mean sABP, dABP, and heart rate (HR), and the daytime sABP, dABP, and HR were similar between the two groups. In contrast, compared

Table 2. Univariate Logistic Regression Analysis with Left Ventricular Hypertrophy (LVH) as the Dependent Variable in Patients with Untreated Essential Hypertension

	LVH		
	Odds ratio	95% CI	*p* value
Age	0.98	0.92–1.06	n.s.
Gender	0.75	0.45–2.20	n.s.
BMI	1.25	0.95–1.64	n.s.
Smoking	1.18	0.67–2.82	n.s.
24-h sABP	1.06	0.98–1.18	n.s.
24-h dABP	1.10	0.98–1.22	n.s.
24-h HR	1.08	0.99–1.20	n.s.
Daytime sABP	1.07	0.98–1.16	n.s.
Daytime dABP	1.08	0.97–1.18	n.s.
Daytime HR	1.09	0.99–1.21	n.s.
Nighttime sABP	1.25	1.06–1.31	<0.0001
Nighttime dABP	1.18	1.07–1.28	0.0021
Nighttime HR	1.08	1.01–1.17	0.0452
Non-dippers	3.96	1.55–10.1	0.0041
T-Chol	0.99	0.97–1.04	n.s.
TGL	1.01	1.00–1.04	0.0279
HDL-C	0.91	0.86–0.96	0.0003
FPG	1.04	1.01–1.07	0.0186
F-IRI	1.54	1.17–2.04	0.0024
HOMA-index	5.04	2.04–12.4	<0.0001
HbA1c	3.71	0.84–14.6	n.s.
Uric acid	2.08	1.19–3.64	0.0103
Creatinine	2.31	0.38–22.5	n.s.
E/*A* ratio	0.86	0.62–0.96	0.0088
Deceleration time	1.02	1.01–1.04	0.0267

Significant predictors of LVH were explored among 3 parameters: gender, smoking and non-dipping status (female=0, male=1; absence=0, presence=1). *E*/*A* ratio, the ratio of peak velocities of early to late ventricular filling. See Table 1 for other abbreviations.

Table 3. Multivariate Logistic Regression Analysis with Left Ventricular Hypertrophy (LVH) as the Dependent Variable in Patients with Untreated Essential Hypertension

	LVH		
	Odds ratio	95% CI	*p* value
HDL-C	0.90	0.85–0.97	0.0422
HOMA-index	3.39	1.20–9.57	0.0210
Nighttime sABP	1.18	1.02–1.29	0.0451

See Table 1 for abbreviations.

to the group without LVH, the group with LVH exhibited a higher nighttime sABP ($p<0.0001$), dABP ($p<0.0001$) and HR ($p=0.0404$). Furthermore, the percentage of non-dipping patients was higher in the group with LVH ($p=0.0034$). When laboratory values were compared between the two groups, the plasma total cholesterol was not significantly different, but the group with LVH had higher triglyceride ($p=0.0221$) and uric acid ($p=0.0062$) levels than the group without LVH. The plasma HDL-C was lower in the group with LVH than in the group without LVH ($p<0.0001$). With respect to glucose homeostasis, the group with LVH also had higher fasting plasma glucose (FPG) levels ($p=0.0144$), insulin concentrations (F-IRI) ($p<0.0001$), and HOMA-index ($p<0.0001$). However, the HbA1c and plasma creatinine were not significantly different between the two groups.

In regard to the echocardiographic findings, when factors related to LV diastolic function were examined, we observed a decreased *E*/*A* ratio (0.98±0.18 *vs*. 0.85±0.15, $p<0.0001$) and increased deceleration time (239±36 *vs*. 270±51 ms, $p=0.0031$) in patients with LVH.

We used univariate logistic regression analysis to determine risk factors for the development of LVH in this patient population, and the risk of LVH was associated with triglyceride levels (odds ratio [OR] 1.01, 95% confidence interval [CI]=1.00–1.04, $p=0.0279$), HDL-C levels (OR 0.91, 95% CI=0.86–0.96, $p=0.0003$), FPG (OR 1.04, 95% CI=1.01–1.07, $p=0.0186$), F-IRI (OR 1.54, 95% CI=1.17–2.04, $p=0.0024$), HOMA-index (OR 5.04, 95% CI=2.04–12.4, $p<0.0001$), uric acid (OR 2.08, 95% CI=1.19–3.64, $p=0.0103$), *E*/*A* (OR 0.86, 95% CI=0.62–0.96, $p=0.0088$), deceleration time (OR 1.02, 95% CI=1.01–1.04, $p=0.0267$), nighttime sABP (OR 1.25, 95% CI=1.06–1.31, $p<0.0001$), nighttime dABP (OR 1.18, 95% CI=1.07–1.28, $p=0.0021$), nighttime HR (OR 1.08, 95% CI=1.01–1.17, $p=0.0452$), and non-dipper status (OR 3.96, 95% CI=1.55–10.1, $p=0.0041$) as the dependent metabolic and echocardiographic and hemodynamic parameters in essential hypertensive patients (Table 2).

Finally, multivariate logistic analysis identified HDL-C (OR=0.90, 95% CI=0.85–0.97, $p=0.0422$), HOMA-index (OR=3.39, 95% CI=1.20–9.57, $p=0.0210$) and nighttime sABP (OR=1.18, 95% CI=1.02–1.29, $p=0.0451$) as significant independent risk factors for the presence of LVH in newly diagnosed patients with essential hypertension (Table 3).

The LVMI was correlated with the HOMA-index (r=0.558, $p<0.0001$) (Fig. 1).

The subjects were divided into four groups based on whether or not they had insulin resistance and their HDL-C levels (Fig. 2).

Group A ($n=31$) included patients with a HOMA-index of less than 2.5 and high HDL-C (≥40 mg/dl for men, ≥50 mg/dl for women); Group B ($n=22$) included patients with a HOMA-index of less than 2.5 and a low HDL-C (<40 mg/dl for men, <50 mg/dl for women); Group C ($n=10$) included patients with a HOMA-index of greater than 2.5 and high HDL-C (≥40 mg/dl for men, ≥50 mg/dl for women); Group D ($n=17$) included patients with a HOMA-index of greater than 2.5 and low HDL-C (<40 mg/dl for men, <50 mg/dl for women). LVMI was higher in Group D than Group A

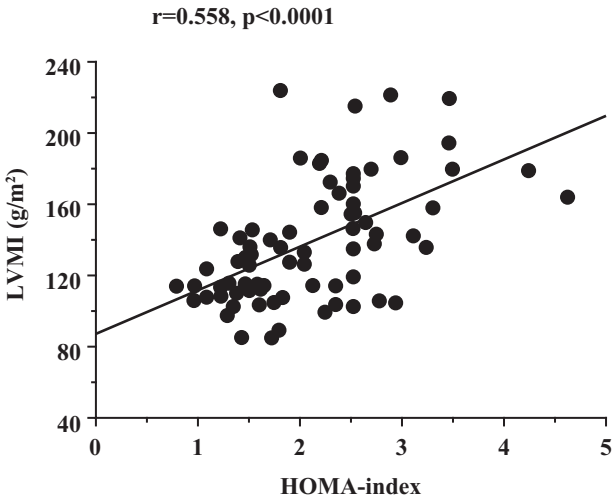

Fig. 1. *Correlations of LVMI with the HOMA-index in untreated essential hypertensive patients.*

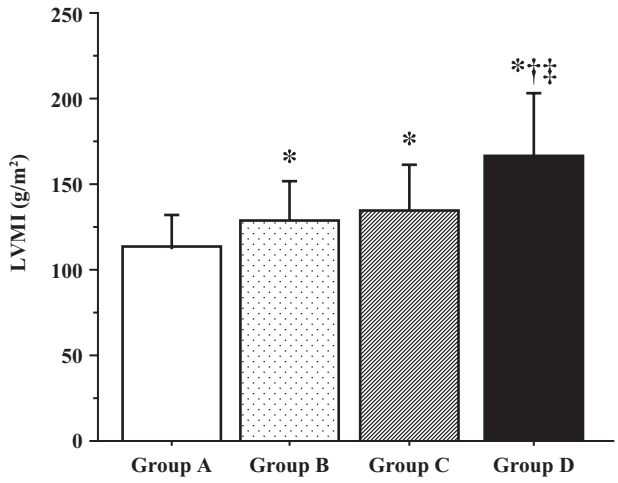

Fig. 2. *Comparison of LVMI among the four groups based on the HDL-C and HOMA-index. Data are the mean±SD. Group A (*n = *31) included patients with a HOMA-index of less than 2.5 and high HDL-C (≥40 mg/dl for men, ≥50 mg/dl for women); Group B (*n = *22) included patients with a HOMA-index of less than 2.5 and a low HDL-C (< 40 mg/dl for men, < 50 mg/dl for women); Group C (*n = *10) included patients with a HOMA-index of greater than 2.5 and high HDL-C (≥40 mg/dl for men, ≥50 mg/dl for women); Group D (*n = *17) included patients with a HOMA-index of greater than 2.5 and low HDL-C (< 40 mg/dl for men, < 50 mg/dl for women).* *p < *0.01 compared with Group A,* †p < *0.01 compared with Group B,* ‡p < *0.01 compared with Group C.*

($p<0.01$), Group B ($p<0.01$), and Group C ($p<0.01$). LVMI was similar in Group B and Group C. LVMI was higher in Group B ($p<0.01$) and Group C ($p<0.01$) than in Group A.

Discussion

LVH is an important clinical finding that arises from and contributes to a number of serious cardiovascular conditions, and is modified by both hemodynamic and nonhemodynamic factors. In patients with newly diagnosed essential hypertension who had not yet undergone treatment, we identified significantly higher glucose metabolic parameters (FPG, F-IRI, HOMA-index), triglyceride, and uric acid in the group with LVH. Furthermore, HDL-C was significantly lower in the patients with LVH than in those without LVH. Additionally, nighttime sABP, dABP, and HR were all significantly higher in patients with LVH compared to those without LVH at the time of diagnosis. When all of these factors were considered by multiple regression analysis, the HOMA-index, HDL-C levels, and nighttime sABP were found to be independent risk factors for the presence of LVH in Japanese patients with newly diagnosed untreated essential hypertension.

Insulin resistance with compensatory hyperinsulinemia is thought to be a critical pathophysiological mechanism underlying the development of the metabolic syndrome (*23*, *24*), and there is a relationship between insulin resistance and LVH in hypertensive subjects (*3*, *4*, *8*). It has been proposed that insulin resistance contributes to the development of LVH through multiple mechanisms including the accentuation of sympathetic nervous system activity (*25*), disordered sodium reabsorption in the kidney (*26*), the growth of smooth muscle cells in blood vessels (*27*) and the generation of insulin growth factor-1 (*28*). We previously showed that hypertensive patients with LVH had a high nighttime HR and ABP, and increased insulin resistance compared with those without LVH (*8*). In an otherwise healthy population, Facchini *et al*. (*29*) observed a significant correlation between elevated nocturnal HR and insulin resistance accompanied with hyperinsulinemia. Consistent with these results, our present study demonstrated an apparent relation between LVH and both the HOMA-index and nighttime HR in hypertensive patients. In the present study, patients with LVH had decreased LV diastolic function compared to those without LVH. We recently demonstrated that LV diastolic function is associated with insulin resistance in type 2 diabetic patients (*30*). Interestingly, development of fibrosis in the myocardial stroma and sclerosis of the left ventricle without LVH has been noted in an animal model of abnormal glucose tolerance, which may provide some insight into the basis of the relationship between insulin resistance and LV diastolic dysfunction (*31*). In addition, Watanabe *et al*. (*4*) reported that insulin resistance accelerates the deterioration of LV diastolic function in patients with essential hypertension.

Our previous study showed that LVH was significantly associated with high nighttime HR as well ABP parameters (24-h mean and nighttime ABP) in non-dipping essential hypertensive patients with high HOMA-index (*8*). In our current study, LVH was associated with high nighttime mean

ABP but not high 24-h mean ABP in hypertensive patients with insulin resistance. In a study of normotensive patients, Hoshide *et al*. (*32*) observed similar 24-h mean BPs between dipping and non-dipping subjects, but the LVMI was higher in the non-dippers. Thus, our results suggest that non-dipping nocturnal ABP, with its link to increased sympathetic activity and insulin resistance, is a more significant contributor to the development of LVH than 24-h mean BP. Indeed, the relation among LV mass measured in the clinic, BP measured in the clinic, and ABP is modest and LV mass is modified by several nonhemodynamic factors, such as neurohormonal and metabolic factors (*33*, *34*).

Recent studies have identified a relationship between LVH and HDL-C in both hypertensive patients and the general population (*9–11*). Our current observations are largely consistent with the published results. However, the present study had an advantage in that we examined ABP monitoring and abnormalities in glucose and insulin metabolism as well as lipid metabolism. These metabolic abnormalities are frequently observed in hypertensive patients and have been shown to accelerate LVH. It is now believed that ABP monitoring is better than BP values for determining the profile and degree of essential hypertension (*33*, *35*).

It is thus essential that all these parameters be examined by multiple regression analysis to identify determinant factors of LVH and to assess the combined influence of these variables in hypertensive subjects with metabolic syndrome. Furthermore, the impact of insulin resistance and HDL-C on the development of LVH is additive in this population (Fig. 1). As a possible explanation for the effects of low HDL-C on cardiac structural and function alternations, therefore, the involvement of insulin resistance and hyperinsulinemia should be considered. In fact, the serum levels of HDL-C are inversely correlated with serum insulin levels (*12*, *13*), and some studies have reported that hyperinsulinemia or insulin resistance is related to LVH in hypertensive patients (*4*). Another possible mechanism is the detrimental effect of low HDL-C levels on endothelial function (*36*), which has been associated, in turn, with LVH in hypertensive patients (*37*).

We did not measure endothelial function in the present study. Further studies are necessary to investigate the role of endothelial function in low HDL-C and LVH and in untreated essential hypertension.

To our knowledge, this is the first report in which multiple regression analysis identified HDL-C, in addition to HOMA-index and nighttime sABP, as an independent predictor for the presence of LVH in newly diagnosed, untreated essential hypertensive patients. There are several limitations to this study. First, it has been reported that there are sex-related differences in the relations of insulin resistance and obesity to LVH in hypertensive patients (*38*). In the present study, there was no significant difference in these measures between male and female subjects (data not shown). A large-scale study will be needed to clarify the gender difference. Secondly, a previous study demonstrated an inverse relationship between nocturnal BP decline and LV mass in a large population of unselected and untreated patients with essential hypertension (*39*). In the present study, nighttime sABP was a significant independent risk factor for the presence of LVH. However, the OR between nighttime sABP and LVH was slightly weak (OR: 1.18). This may have been due to the relatively small number of patients in our study. Finally, although hypertension is associated with the visceral fat area, we did not employ abdominal computed tomography in the present study. Therefore, we must further evaluate the relationship between LVH and the visceral fat area in hypertensive patients.

In conclusion, our findings demonstrated that HOMA-index, HDL-C level and nighttime sABP are independent predictors for the presence of LVH in Japanese patients with untreated essential hypertension.

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