

## ORIGINAL ARTICLE

# Inappropriateness of ventricular hypertrophy is important as a determinant of BNP but not of diastolic filling in untreated hypertensive patients

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Echocardiographically determined inappropriateness of left ventricular mass (LVM) is an independent risk factor for cardiovascular events. Although LV hypertrophy is associated with an increase in the plasma brain natriuretic peptide level and decreased LV diastolic filling, it is unknown whether the inappropriateness of LVM affects them. We studied 77 untreated hypertensive patients (49 men, 28 women, aged  $59 \pm 12$  years). The plasma brain natriuretic peptide level was measured, in addition to routine echo Doppler indexes of LV geometry and function. The appropriateness of LVM to cardiac workload was evaluated by the ratio of the observed LVM to the value predicted for individual sex, stroke work and height<sup>2,7</sup> (oLVM/pLVM). Multivariate analysis showed that the plasma brain natriuretic peptide level increased with LVM index but decreased when oLVM/pLVM increased. The ratio of the peak early diastolic flow velocity of mitral flow to the peak early diastolic velocity of mitral annulus (E/E') correlated not only with oLVM/pLVM but also with the LVM index ( $r=0.30$ ,  $P<0.05$ ;  $r=0.37$ ,  $P<0.05$ , respectively). However, when a multiple stepwise regression analysis was carried out, only LVM index was determined to be a significant correlate of the E/E' ratio, indicating that the inappropriateness of LVM does not affect the E/E' ratio in hypertensive patients. Brain natriuretic peptide levels are influenced not only by the extent of LV hypertrophy but also by the inappropriateness of hypertrophy in untreated hypertensive patients. Diastolic filling is mostly affected by the extent of LV hypertrophy and not by the appropriateness of hypertrophy.

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## INTRODUCTION

Left ventricular (LV) hypertrophy develops as an adaptive mechanism to increased load in hypertensive patients. However, it is well known that the extent of LV hypertrophy does not necessarily correlate with the extent of load increase or with the duration of hypertension in individual patients. There are some load-independent mechanisms of LV hypertrophy; for example, activation of neurohumoral hormones, such as the renin–angiotensin–aldosterone system and endothelin pathways, induces LV hypertrophy.<sup>1</sup> Thus, it is considered to be important to assess the extent of LV hypertrophy in proportion to increased load and to consider whether it is an adaptive mechanism in individual patients. Recently, it was postulated that echocardiography is useful in determining the appropriateness of LV hypertrophy.<sup>2</sup> In this determination, predicted LV mass is calculated from stroke work, from the height and gender of individual patients and from the ratio of actual LV mass (LVM) to the predicted value used as an index of LV hypertrophy inappropriateness. Inappropriate LVM is indicative of a risk of cardiovascular events either in the presence or in the absence of

LV hypertrophy, which was traditionally defined by LVM index or wall thickness.<sup>3,4</sup> Thus, the concept of inappropriate LVM sheds light on the quality rather than the quantity of LV hypertrophy in hypertensive patients.

Plasma brain natriuretic peptide (BNP) levels are known to be elevated in hypertensive patients compared with that in normotensive patients, even if the patients have no symptoms of heart failure.<sup>5</sup> Plasma BNP levels are strongly correlated with LVM index (LVMI) in hypertensive patients; however, the effect of the appropriateness of LVM on the relationship is unclear. The suboptimal correlation between plasma BNP level and LVMI may be explained by variability in the appropriateness of LV hypertrophy among patients. Meanwhile, LV diastolic function or filling deteriorates in patients with hypertension and/or LV hypertrophy;<sup>6</sup> there is also a relationship between the abnormalities of LV diastolic filling and the extent of LV hypertrophy. Similarly, this may be explained as an effect of the appropriateness of LVM. Thus, we hypothesized that the appropriateness or inappropriateness of LVM modifies the interrelation of LVMI, plasma BNP level

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and LV diastolic filling. Our study attempted to clarify this hypothesis. This was a study of untreated hypertensive patients, in contrast to most of the previous studies, in which data were collected during treatment or shortly after treatment stopped. Any hypertensive medication should largely affect the relationship between LV geometry and function. Therefore, we were able to assess the effects of LV geometry and diastolic function on plasma BNP level independent of the influence of medication.

## METHODS

### Patients

We enrolled 77 patients who visited our hospital because of essential hypertension between April 2004 and March 2007. Hypertension was defined as systolic blood pressure level of 140 mm Hg or higher, diastolic blood pressure level of 90 mm Hg or higher or both. Symptoms or signs of heart failure were absent in the patients, and none had been treated for hypertension. A diagnosis of essential hypertension was confirmed by medical history, physical examination and hormone measurements (plasma rennin activity, aldosterone level and catecholamine level). There were 29 women and 48 men, with a mean age of 59 years. All patients had normal renal function (plasma serum creatinine < 1.0 mg per 100 ml) and sinus rhythm. Conventional transthoracic echocardiography was conducted and plasma BNP level was measured before treatment.

### Assays for BNP

All samples were collected from veins and placed in ethylenediaminetetraacetic acid (EDTA) tubes, which were immediately placed on ice and analyzed within 24 h. Plasma levels of BNP were measured using a highly sensitive immunoradiometric assay (Shiono RIA BNP assay kit, Shionogi, Osaka, Japan).

### Echocardiographic study

Transthoracic echocardiographic studies were conducted to measure left atria and LV cavity sizes and LV wall thickness with M mode and two-dimensional echocardiography, as previously described.<sup>7</sup> Observed LVM and relative wall thickness (RWT) were estimated using the following formula:

$$\text{Observed LVM} = 0.8 \times 1.04 \times \{(\text{IVSth} + \text{LVDD} + \text{PWth})^3 - \text{LVDD}^3\} + 0.6$$

$$\text{Relative wall thickness (RWT)} = \text{PWth} \times 2 / \text{LVDD}$$

where LVDD represents end-diastolic diameter and PWth represents the thickness of the posterior wall. In addition, predicted LVM was calculated as follows:<sup>3</sup>

$$\text{Predicted LVM} = 55.37 + 0.64 \times \text{stroke work} + 6.63 \times \text{height} \times 2.7 - 18.1 \times \text{gender}$$

where gender is coded as 1=male and 2=female.

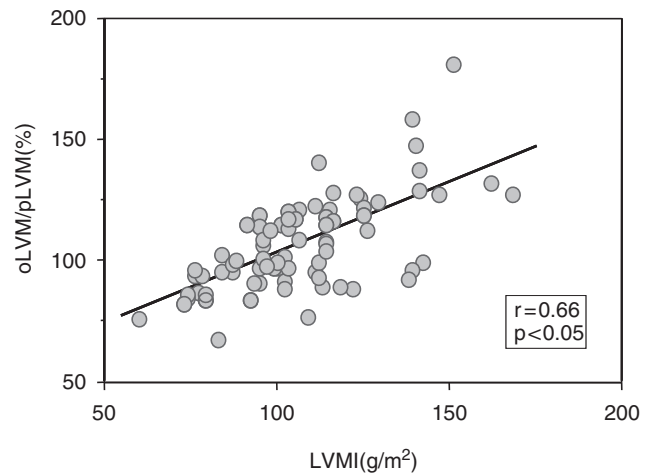
$$\text{Stroke work} = \text{systolic blood pressure} \times \text{stroke volume} \times 0.0144$$

These were provided for the calculation of an index of inappropriateness of LVM, the ratio of observed LVM to predicted LVM (oLVM/pLVM) expressed as a percentage. LV end-diastolic and end-systolic volumes were calculated using Teicholz's correction of the cube formula.

Pulsed Doppler transmitral flow velocity pattern was recorded using an apical three-chamber view. Sample volume was placed at the tip of mitral leaflets. The peak velocity of the early diastolic wave (E) was measured over three to five consecutive cardiac cycles. We also measured the early diastolic maximal peak velocity of the septal mitral annular movement (E') using the tissue Doppler image. We took E/E' as an index of LV diastolic function.

### Statistical analysis

Values are expressed as mean  $\pm$  s.d. The association between two variables was assessed by a simple linear regression analysis. Multiple stepwise linear regression analysis was carried out to assess the significant independent factors that may affect a given variable.



**Figure 1** There was a significant correlation between observed LVM to predicted LVM (oLVM/pLVM) and LVMI index (LVMI) in untreated hypertensive patients ( $P < 0.05$ ). LVM, left ventricular mass.

## RESULTS

There was a significant correlation between LVMI and oLVM/pLVM ( $r = 0.66$ ,  $P < 0.05$ ; Figure 1). We divided the patients into two groups using the median value of oLVM/pLVM (that is, 100). Clinical characteristics and echocardiographic data of the two groups are shown in Table 1.

### Plasma BNP level

The plasma BNP level was correlated with LVMI ( $r = 0.27$ ,  $P < 0.05$ ; Figure 2). By contrast, there was no significant correlation between the plasma BNP level and oLVM/pLVM ( $r = 0.01$ ,  $P = 0.99$ ). When multiple stepwise regression analysis was carried out, both variables were selected as significant independent correlates of the plasma BNP level (Table 2). The findings of this analysis indicate that plasma BNP level increases as LVMI increases, and decreases as oLVM/pLVM increases.

### LV diastolic filling

The E/E' ratio correlated not only with oLVM/pLVM but also with LVMI ( $r = 0.30$ ,  $P < 0.05$ ,  $r = 0.37$ ,  $P < 0.05$ , respectively, in Figure 3). However, when multiple stepwise regression analysis was carried out, only LVMI was selected as a significant correlate of the E/E' ratio (Table 3), indicating that the inappropriateness of LVM does not affect the E/E' ratio in hypertensive patients. There was no significant correlation between E/A (the ratio of the peak velocity of the early diastolic wave to the peak velocity of the atrial contraction wave) and LVMI ( $r = -0.04$ ,  $P = \text{NS}$ ) or between E/A and oLVM/pLVM ( $r = 0.05$ ,  $P = \text{NS}$ ).

We also analyzed data obtained from 45 hypertensive patients after 6 months of treatment. There were similar tendencies in the relationship between BNP and hypertrophy, but the relationship did not reach statistical significance (BNP vs. LVMI  $r = 0.23$ ,  $P = \text{NS}$ ; BNP vs. oLVM/pLVM,  $r = -0.03$ ,  $P = \text{NS}$ ). There was no correlation between diastolic filling and LV hypertrophy (E/E' vs. LVMI,  $r = 0.08$ ,  $P = \text{NS}$ , E/E' vs. oLVM/pLVM,  $r = 0.06$ ,  $P = \text{NS}$ ).

## DISCUSSION

This study clearly showed that plasma BNP level is affected not only by the extent but also by the inappropriateness of LV hypertrophy. By

contrast, diastolic filling is influenced by the extent but not by the inappropriateness of LV hypertrophy.

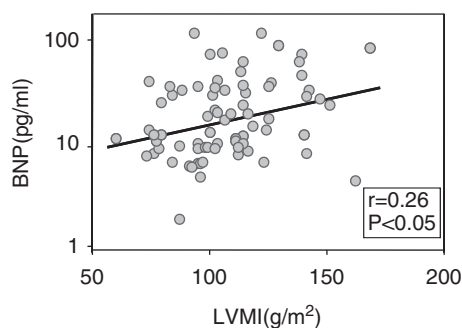
### BNP and LV hypertrophy

Univariate analysis showed that plasma BNP level correlated with LVMI but not with oLVM/pLVM in untreated hypertensive patients. However, when multiple stepwise regression analysis was carried out, the plasma BNP level was independently affected not only by LVMI but also by the inappropriateness of LVM. The increase in the inappropriateness of LVM tended to correlate with a lower plasma BNP level. This trend was not evident in the univariate analysis, and should have been masked by the substantial positive correlation between LVMI and oLVM/pLVM.

**Table 1 Clinical characteristics and echocardiographic data of two groups**

	oLVM/pLVM ≤ 100	oLVM/pLVM > 100
Number	38	39
Age, years	59 ± 12	58 ± 13
Gender, F/M	13/25	16/23
BSA, m <sup>2</sup>	1.6 ± 0.2	1.7 ± 0.2
SBP, mm Hg	167 ± 20	158 ± 16 <sup>a</sup>
DBP, mm Hg	95 ± 13	93 ± 9
HR, beats per minute	65 ± 9	66 ± 10
CRE, mg per 100 ml	0.68 ± 0.14	0.70 ± 0.14
eGFR, ml min <sup>-1</sup> per 1.73 m <sup>2</sup>	84 ± 16	80 ± 17
BNP, pg ml <sup>-1</sup>	26 ± 29	26 ± 22
LAD, mm	36 ± 5	39 ± 6 <sup>a</sup>
Systolic wall stress	49 ± 12	45 ± 12
LVMI, g m <sup>-2</sup>	96 ± 19	117 ± 20 <sup>a</sup>
RWT	0.38 ± 0.03	0.43 ± 0.05 <sup>a</sup>
E, cm s <sup>-1</sup>	63 ± 14	60 ± 13
A, cm s <sup>-1</sup>	71 ± 14	68 ± 15
E/A	0.91 ± 0.28	0.93 ± 0.29
DcT, ms	205 ± 49	209 ± 39
E', cm s <sup>-1</sup>	5.9 ± 1.3	5.4 ± 1.4
E/E'	11 ± 3	12 ± 3

Abbreviations: BNP, brain natriuretic peptide; BSA, body surface area; CRE, serum creatinine; DBP, diastolic blood pressure; DcT, deceleration time of E wave; E, peak early diastolic flow velocity of mitral flow; E', peak early diastolic velocity of mitral annulus; E/A, the ratio of E to A; E/E', the ratio of E to E'; eGFR, estimated glomerular filtration rate; F, female; HR, heart rate; LAD, left atrial dimension; LVMI, left ventricular mass index; M, male; oLVM, observed left ventricular mass; pLVM, predicted left ventricular mass; RWT, relative wall thickness; SBP, systolic blood pressure.  
<sup>a</sup>P < 0.05 vs. oLVM/pLVM ≤ 100.



One might expect the plasma BNP level to increase with the inappropriateness of LVM. LV hypertrophy is an independent risk factor of the cardiovascular complications of hypertension as evidenced in the Framingham study, and it has also been suggested that inappropriate LVM may represent an accelerated phase of transition from compensated LV hypertrophy toward heart failure.<sup>8,9</sup> However, the plasma BNP level tended to decrease as the inappropriateness of LVM increased. This finding may be explained by the dependence of BNP secretion on LV wall stress. Systolic LV wall stress increases with blood pressure, causing wall thickening, that is, LV hypertrophy, which in turn works to normalize the increased wall stress to prevent after-load mismatch. If LV hypertrophy develops inappropriately, systolic LV wall stress may decrease even below the normal range. Thus, systolic wall stress should be an important factor affecting the plasma BNP level in untreated hypertensive patients. Therefore, the association of LV hypertrophy with a comparable elevation in the plasma BNP level may indicate that LV hypertrophy is a result of an adaptive mechanism. In such cases, blood pressure lowering would probably reduce LV hypertrophy and decrease the plasma BNP level. Recently, Lopez *et al.*<sup>10</sup> found that circumferential end-systolic wall stress in untreated hypertensives is even higher in patients with inappropriate LV mass than in those with appropriate LV mass. If so, we may have to consider not only systolic but also diastolic wall stress as correlates of the plasma BNP level. By contrast, if the plasma BNP level is lower than expected in patients with hypertensive hypertrophy, LV hypertrophy is not solely due to an adaptive mechanism, and after-load reduction alone may be insufficient to reduce LV hypertrophy and plasma BNP level.

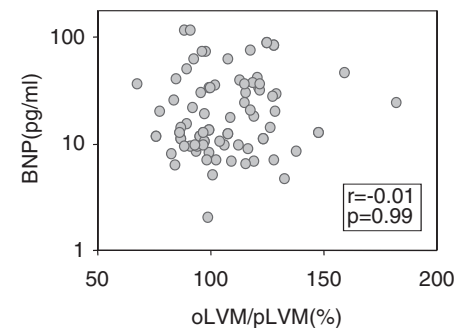
### Diastolic filling and LV hypertrophy

The mitral E/A ratio has been widely used as an index of LV diastolic filling. Unfortunately, this index is load dependent, and more recently, E/E' has been preferred as a relatively load-independent index of LV diastolic filling. As LV diastolic dysfunction advances, E/E' increases. Both LVMI and oLVM/pLVM were correlated with the E/E' ratio. However, oLVM/pLVM was not selected in the multiple stepwise

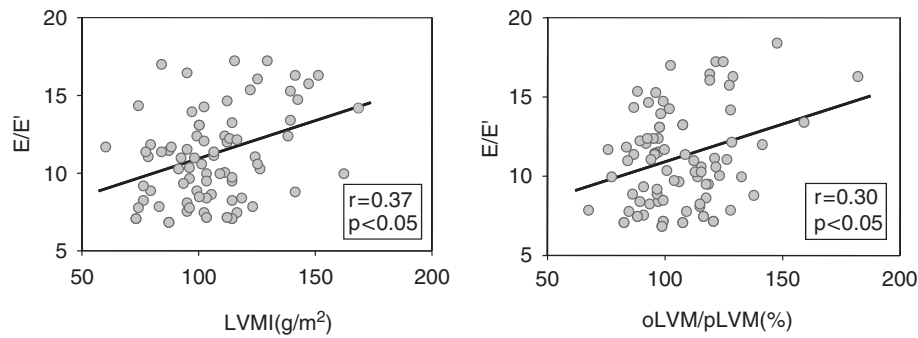
**Table 2 Multiple stepwise regression analysis for BNP**

	Standardized coefficient $\beta$ (s.e.)	P-value
oLVM/pLVM	0.51 (0.17)	0.001
LVMI	-0.33 (0.19)	0.023

Abbreviations: BNP, brain natriuretic peptide; LVMI, left ventricular mass index; oLVM, observed left ventricular mass; pLVM, predicted left ventricular mass.



**Figure 2** Logarithmic brain natriuretic peptide (BNP) was plotted against left ventricular mass index (LVMI) (left panel) and against observed LVM to predicted LVM (oLVM/pLVM) (right panel). Logarithmic BNP was higher when LVMI increased, whereas there was no correlation between logarithmic BNP and oLVM/pLVM.



**Figure 3** The ratio of the peak early diastolic flow velocity of mitral flow to the peak early diastolic velocity of mitral annulus (E/E') was plotted against left ventricular mass index (LVMI) (left panel) and against observed LVM to predicted LVM (oLVM/pLVM) (right panel). E/E' was higher when LVMI and oLVM/pLVM increased ( $P<0.05$ ).

**Table 3** Multiple stepwise regression analysis for E/E'

	Standardized coefficient $\beta$ (s.e.)	P-value
LVMI	0.37 (0.014)	0.01

Abbreviations: E, peak early diastolic flow velocity of mitral flow; E', peak early diastolic velocity of mitral annulus; E/E', the ratio of E to E'; LVMI, left ventricular mass index.

regression analysis, indicating that the inappropriateness of LV hypertrophy does not affect the E/E' ratio in untreated hypertensive patients. The significant correlation between oLVM/pLVM and the E/E' ratio in univariate analysis may be explained by the correlation between LVMI and oLVM/pLVM. This finding indicates that the extent of LV hypertrophy is an important factor affecting LV diastolic filling, and that the quality or inappropriateness of LV hypertrophy is not an important factor in untreated hypertensive patients. It is well known that the relationship between the extent of LV hypertrophy and diastolic filling is extremely complex in patients with hypertrophic cardiomyopathy.<sup>11</sup> In addition to hypertrophy, the activation of the sympathetic nervous system may influence the LV diastolic function. Future studies are necessary to clarify the complex relationship between LV hypertrophy and diastolic filling.

It is generally accepted that plasma BNP level is not a sufficient screening measure for LV hypertrophy in untreated hypertensive patients. The results of this study suggest that the inappropriateness of LVM may at least partially account for the weakness of the plasma BNP level as a predictor of LV hypertrophy. The inappropriateness of LVM is evaluated by individual stroke work, height and gender. Although this measure reflects individual characteristics, there was only a weak correlation between oLVM/pLVM and LV diastolic function. Although the inappropriateness of LVM may help clarify the pathophysiology of hypertrophy, its impact on LV diastolic function seems to be much smaller than expected in untreated hypertensive patients. In this context, conventional LVMI may be more important than its inappropriateness.

We also studied data collected 6 months after the patients were treated. There was no significant correlation between BNP and LV hypertrophy, or between diastolic filling and LV hypertrophy. Clearly, hypertensive medication strongly affects the relationship between LV geometry and function. Thus, the implications of the inappropriateness of LVM may be different in untreated and treated hypertensive patients.

### Study limitations

Two limitations of our study are noted. First, LV diastolic performance was assessed only using echo Doppler parameters. Second, LV mass was assessed with M-mode rather than with two-dimensional or three-dimensional echocardiography. However, no patient had wall motion abnormalities or asymmetric hypertrophy, and the error in measurements of LV mass should be minimal.

In conclusion, the increased plasma BNP level was influenced not only by the extent of LV hypertrophy but also by the quality or inappropriateness of the hypertrophy in untreated hypertensive patients. By contrast, LV diastolic filling was mostly affected by the extent of LV hypertrophy and not by the inappropriateness of the hypertrophy.

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