Enhanced Radial Late Systolic Pressure Augmentation in Hypertensive Patients With Left Ventricular Hypertrophy

Junichiro Hashimoto, Daisuke Watabe, Rieko Hatanaka, Tomohiro Hanasawa, Hirohito Metoki, Kei Asayama, Takayoshi Ohkubo, Kazuhito Totsune, and Yutaka Imai

Background: Wave reflection augments central blood pressure (BP) in late systole, thus increasing cardiac afterload. We examined the relationship between late systolic pressure augmentation in the peripheral radial artery pulse wave and the existence of left ventricular hypertrophy (LVH) in hypertension.

Methods: Brachial BP, radial augmentation index (AIr), and carotid-femoral pulse wave velocity (PWVcf) were determined in 77 untreated hypertensive patients aged 56 ± 10 years. Cardiac structure and function were assessed by ultrasound, and LVH was defined based on the LV mass index (LVMI). Using multivariate analysis, patient characteristics were compared between those with (+) and without (−) LVH.

Results: The LVMI was correlated independently and positively with AIr (β = 0.33, P = .004) and the brachial mean arterial pressure (MAP; β = 0.25, P = .03). The ratio of early to atrial peak velocities (E/A ratio) of the diastolic transmitral flow tended to be correlated negatively with the AIr. The LVH (+) group had a significantly higher AIr than the LVH (−) group [LVH (+), 97%; LVH (−), 89%; P = .003]; this difference remained significant even after adjustment for age, gender, MAP, and heart rate. The adjusted relative risk of LVH was 1.99 for each 10% AIr increase (P = .005). In contrast, LVMI was not correlated with the PWVcf, and the PWVcf was not different between the LVH (+) and LVH (−) groups. Moreover, there was no significant correlation between PWVcf and AIr.

Conclusions: These results suggest that the peripheral AIr measurement is clinically useful in predicting LVH. Enhanced wave reflection may be related to the development of LVH in hypertensive patients. Am J Hypertens 2006;19:27–32 © 2006 American Journal of Hypertension, Ltd.

Key Words: Left ventricular hypertrophy, radial pulse wave, wave reflection, augmentation index, hypertension.

Left ventricular hypertrophy (LVH) is a powerful independent cardiovascular risk factor and the most common cardiac abnormality associated with hypertension. The development of LVH is generally ascribed to hemodynamic overload of the heart. However, previous studies have shown that the LV mass index (LVMI) is not necessarily correlated with conventionally measured brachial artery blood pressure (BP). One possible explanation for the lack of correlation might be that the cardiac afterload depends on the central aortic BP rather than on the peripheral brachial BP.

The BP pulse waveform is generated by the superposition of the reflected backward wave on the incident forward wave. The early wave reflection that returns in late systole augments the BP in the ascending aorta. It has been proposed that this late systolic pressure augmentation could increase cardiac afterload. In fact, a few studies have shown that this augmentation, which is described by the augmentation index (AI), is associated with particular left ventricular structure characteristics in normotensive subjects and hemodialysis patients. However, in essential hypertension there are little clinically relevant data about...
the relationship between late systolic augmentation and LVH.

The amplitude and the timing of the wave reflection are closely associated with arterial compliance. Various pulse wave-based indices, including pulse wave velocity (PWV) and AI, have been used as noninvasive measures of arterial structure and function. These different indices appear to provide different information about arterial properties, as PWV depends on regional large artery stiffness, whereas AI depends not only on systemic arterial elasticity but also on arterial geometry and tone. However, it is not yet fully understood how these measurements relate to the cardiac and arterial changes seen in various disease states.

To date, central aortic augmentation has been evaluated noninvasively by mathematically transforming the radial artery pulse waveform to the aortic pulse waveform. Recent research has demonstrated that the central AI (AI_{c}) could be estimated by the radial AI (AI_{r}) directly without the need for a transfer function. Thus, in the present study, we measured AI_{c} in hypertensive patients to examine the association between radial late systolic pressure augmentation and LVH. We also compared carotid-femoral PWV (PWV_{cf}) and AI_{r} with respect to their relevance to cardiac structure.

**Methods**

**Study Subjects**

The subjects included 77 consecutive, untreated patients with essential hypertension seen at Kojinkai Central Clinic, Sendai, Japan. With the patient in the sitting position, the BP was measured three times. Hypertension was defined as a mean systolic BP ≥140 mm Hg or a mean diastolic BP ≥90 mm Hg. None of the subjects had a previous history of major cardiovascular complications, renal insufficiency (serum creatinine >2 mg/dL), or severe underlying diseases. None of the patients was taking any vasoactive drugs. Informed consent was obtained from all subjects participating in the study, and the study was approved by the institutional review board.

**BP and Pulse Wave Measurements**

All measurements were conducted in a quiet room kept at a constant temperature. First, after a 5-min rest and with the subject seated, brachial BP was measured using an automatic cuff oscillometric device (HEM-907, Omron Healthcare, Kyoto, Japan). Two-dimensionally guided M-mode echocardiography was performed using a ProSound SSD-5500 (Aloka, Tokyo, Japan) with a 3-MHz transducer. Left ventricular dimensions were measured according to the recommendations of the American Society of Echocardiography, and left ventricular mass (LVM) was calculated using the Penn...
convention. The LVM index (LVMI) was calculated by dividing LVM by the body surface area. According to a previous study by Devereux et al., LVH was defined as LVMI >118 g/m² for men and LVMI >108 g/m² for women. The LV ejection fraction (EF) and the fractional shortening (FS) were also examined as measures of cardiac function. In addition, a pulsed-wave Doppler recording was made to determine the early peak (E) and the atrial peak (A) of the diastolic transmitral flow velocity, and to calculate their ratio (the E/A ratio).

Statistical Analysis

First, Pearson’s correlation coefficient was calculated for LVMI and various other parameters. Multivariate regression analysis was used successively to evaluate the independence of the relationship between AIr and LVMI with respect to other confounding variables. Covariates entered into the stepwise model included: age, gender, body height, body mass index (BMI), brachial MAP (or systolic BP), heart rate (HR), biochemical parameters, treatment of diabetes, and treatment of hypercholesterolemia. To compare the effects of the AIr and the brachial systolic BP on LVMI, tertile group differences were tested using analysis of variance (ANOVA) and Scheffe’s post hoc test.

Next, the subjects were divided into two groups according to the presence (+) or absence (−) of LVH. Differences between the two groups were compared using Student t test and χ² test when appropriate. Then, the difference in the AIr between the groups was further evaluated by analysis of covariance (ANCOVA) using age, gender, MAP, and HR as covariates. The effect of increasing AIr on the risk of LVH was examined by logistic regression analysis.

Data are expressed as means ± SD or percentage, unless stated otherwise. Differences at P < .05 were considered statistically significant. All statistical analyses were performed using SPSS version 11.0 software (SPSS Inc., Chicago, IL).

Results

Baseline characteristics of the subjects are shown in Table 1. There were 54 men and 23 women with a mean age of 56 ± 10 years (range, 27 to 75 years). The mean systolic BP was 160 mm Hg, and the mean diastolic BP was 96 mm Hg. Of the 77 subjects, 8 subjects had diabetes, and 1 of these 8 was treated with a sulfonylurea agent. Hypercholesterolemia was present in 17 subjects, and 9 of these patients were treated with statins.

On univariate analysis, LVMI was correlated significantly and positively with AIr (r = 0.29, P = .01). The LVMI was also correlated positively with brachial systolic BP (r = 0.24, P = .04) and age (r = 0.23, P = .05), whereas it was not correlated with MAP, diastolic BP, body height, or BMI. Neither LVMI nor AIr was correlated with brachial PP. The LVMI was negatively correlated with the HR (r = −0.24, P = .04). The LVMI was not significantly different between male and female subjects (121 ± 20 g/m² v 119 ± 28 g/m²). There were no significant correlations between LVMI and biochemical parameters (such as serum creatinine, total cholesterol, HDL-cholesterol, and fasting blood glucose). In contrast to AIr, PWVcf did not correlate with LVMI (r = 0.11). In addition, no significant correlation was observed between AIr and PWVcf (r = 0.14). Echocardiographic parameters of LV systolic function, including EF and FS, were not

<table>
<thead>
<tr>
<th>Table 1. Clinical characteristics of the subjects</th>
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<tbody>
<tr>
<td>All Subjects (n = 77)</td>
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<td>-----------------------</td>
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<tr>
<td>Age (yr)</td>
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<tr>
<td>Gender (male, %)</td>
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<tr>
<td>Body height (cm)</td>
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<tr>
<td>Body mass index (kg/m²)</td>
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<td>Systolic blood pressure (mm Hg)</td>
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<td>Diastolic blood pressure (mm Hg)</td>
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<td>Mean arterial pressure (mm Hg)</td>
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<td>Pulse pressure (mm Hg)</td>
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<tr>
<td>Hypercholesterolemia (%)</td>
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<tr>
<td>Radial augmentation index (%)</td>
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<tr>
<td>Carotid–femoral PWV (m/s)</td>
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</table>

LVH = left ventricular hypertrophy; PWV = pulse wave velocity; NS = not significant.

P values for comparisons between LVH (-) and LVH (+) groups.
correlated with AIr. The diastolic A filling velocity was significantly correlated with AIr ($r = 0.26, P = .02$), although the E velocity was not. As a result, the E/A ratio tended to be negatively correlated with AIr ($r = -0.22, P = .058$).

Multivariate stepwise linear regression analysis revealed that LVMI was independently correlated only with AIr ($\beta = 0.30, P = .007$), along with systolic BP ($\beta = 0.25, P = .02$). The LVMI was not independently related to age, gender, body height, BMI, HR, biochemical parameters, or the treatment of diabetes or hypercholesterolemia.

When the subjects were classified into tertile groups according to the AIr level, LVMI was significantly different among the groups (Fig. 2). The highest and the middle AIr tertiles had a greater LVMI than did the lowest AIr tertile. On the other hand, when the subjects were classified by brachial systolic BP, LVMI did not differ significantly among the tertile groups.

The subject characteristics of LVH (+) and LVH (−) groups are shown in Table 1. Although the LVH (+) group was slightly older than the LVH (−) group, there were no other differences in baseline characteristics. The AIr was greater in the LVH (+) group than in the LVH (−) group. This difference was highly statistically significant, and remained significant even after adjustment for age alone ($P = .02$) or for multiple covariates including age, gender, MAP, and HR ($P = .04$). Similar significance was noted when MAP was replaced with systolic BP as a covariate ($P = .04$). In contrast, PWVcf did not differ between the LVH (+) group and the LVH (−) group (Table 1).

Univariate and multivariate logistic regression analyses revealed that the risk of LVH was elevated about twofold for each 10% increase in the AIr (Table 2). Even after controlling for potentially relevant factors, an increase in the AIr was found to be a significant independent risk factor for LVH.

**Discussion**

The present study demonstrated that LVMI is correlated independently with AIr in untreated hypertensive patients.

### Table 2. The relative risk of left ventricular hypertrophy for each 10% increase in the radial augmentation index (logistic regression analysis)

<table>
<thead>
<tr>
<th>Model</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1 (unadjusted)</td>
<td>1.99</td>
<td>1.23–3.23</td>
<td>.005</td>
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<tr>
<td>Model 2 (age and gender adjusted)</td>
<td>1.84</td>
<td>1.20–3.29</td>
<td>.007</td>
</tr>
<tr>
<td>Model 3 (adjusted for age, gender, MAP, and HR)</td>
<td>1.84</td>
<td>1.04–3.25</td>
<td>.035</td>
</tr>
<tr>
<td>Model 4 (multiple adjusted)*</td>
<td>1.83</td>
<td>1.01–3.32</td>
<td>.047</td>
</tr>
<tr>
<td>Model 5 (multiple adjusted, stepwise)*</td>
<td>1.99</td>
<td>1.23–3.23</td>
<td>.005</td>
</tr>
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</table>

CI = confidence interval.

* Adjusted for age, gender, body mass index, mean arterial pressure (MAP), heart rate (HR), fasting blood glucose, total cholesterol, HDL cholesterol, treatment for diabetes, and treatment for hyperlipidemia.
Even when controlled for other possible relevant factors, patients with LVH had a significantly greater AIr than those without LVH. The adjusted relative risk of LVH was approximately doubled for each 10% increase in the AIr. In contrast, there was no relationship between LVH and PWVcf. To our knowledge, this study is the first to demonstrate a significant association between AIr and LVH in essential hypertension.

In this study, we used AIr as a surrogate for central augmentation index (Alc) to examine the potential influence of late systolic pressure augmentation on the development of LVH. The rationale for the use of peripheral AIr was a recent report by Millasseau et al showing a strong linear correlation between AIr and the AIc, estimated by a generalized transfer function. Taking this finding into account, our results indicate that even an untransformed radial pulse wave can, by itself, provide information about the LV load, as it is influenced by central late systolic augmentation. Alternatively, it is also possible that, in subjects that develop LVH, hypertrophy of the myocardium is accompanied by hypertrophy of vascular smooth muscle in the small arteries, which are the ones that determine pressure wave reflection. Although the use of AIr rather than Alc is a departure from the usual approach, the current results suggest that this simple approach would be clinically applicable.

Our tertile group analyses showed that the AIr had a closer association with LVMI than did brachial systolic BP. Furthermore, despite having similar brachial systolic BP levels, patients with LVH showed a significantly higher AIr than those without LVH. Recently, Pauca et al demonstrated that in hypertensive patients the second peak, but not the first peak, of the radial artery pressure wave corresponds with the aortic systolic BP. This result implies that the radial late systolic pressure peak that is augmented by wave reflection, rather than the radial early systolic peak pressure (corresponding to the radial systolic BP, in most cases) that is little influenced by wave reflection, represents the aortic systolic BP, which determines the LV load. In this connection, Vlachopoulos et al showed that late systolic augmentation significantly contributes to the elevation of central systolic BP, does not affect peripheral systolic BP, but does affect peripheral late systolic peak pressure. These previous observations are concordant with our present results. This suggests that including the evaluation of peripheral late systolic augmentation could provide a more reasonable noninvasive method for estimating LV load than measuring brachial systolic BP alone.

There was an interesting tendency for the diastolic E/A ratio to be negatively correlated with AIr. Central augmentation delays the systolic peak of the pressure wave, and the delay in the systolic peak and the degree of augmentation have been shown to correlate with delayed diastolic ventricular relaxation. Therefore, this observation suggests that enhanced pressure augmentation might affect myocardial relaxation during early diastole and hence lead to diastolic dysfunction. However, it is also possible that LVH by itself may be involved in diastolic dysfunction.

Of note, we found that AIc significantly correlated with LVMI, whereas PWVcf did not. Furthermore, the AIr was a better diagnostic indicator of LVH than PWVcf. The different relationships of AIr and PWVcf to cardiac structure that were found in our study could be explained by assuming that these two measurements provide different information about arterial structure and function. In fact, we observed no significant correlation between AIr and PWVcf in the present study population. This lack of correlation between AIr and PWVcf suggests that, at least in hypertensive subjects, AIr is determined to a much greater extent by the amount of the pressure wave reflection than by its timing. In addition, it is generally thought that the PWVcf offers information about the regional stiffness of the arterial segment under investigation, whereas the AIr is thought to offer information about systemic arterial elasticity, geometry, and tone. Therefore, our results indicate that the interaction between the vascular tree and the left ventricle (namely, the ventricular–vascular interaction) depends on the entire array of arterial properties (as expressed by AIr) rather than on segmental large arterial properties (as expressed by PWVcf). It also seems likely that, in our untreated hypertensive patients, the influence of the wave reflection on late systolic augmentation was determined primarily by the reflection coefficient dependent on the state of distal vasoconstriction and geometry rather than by central arterial stiffening.

There are some limitations to the present study. First, the observed association between AIr and LVMI was relatively modest in a limited number of subjects. Second, we did not measure AIc or central BP. Therefore, although the peripheral AIr showed a closer association with LVMI than did the brachial systolic BP, we could not determine whether central systolic BP or Alc would better correlate with LVMI. Finally, because this study was cross-sectional, the causal relationship between AIr and LVH remains to be fully established. Prospective studies are necessary to resolve this important issue.

In conclusion, our present results suggest that enhanced wave reflection, as shown by an increase in the AIr, is closely related to LVH in hypertensive patients. There is increasing evidence that various antihypertensive drug classes have different effects on reducing late systolic pressure augmentation. Thus, the current findings warrant future studies that would clarify whether antihypertensive treatment designed specifically to reduce augmentation could substantially contribute to the regression of LVH.

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