Left Ventricular Hypertrophy and Geometry in Untreated Essential Hypertension is Associated With Blood Levels of Aldosterone and Procollagen Type III Amino-Terminal Peptide

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Background The present study examined the role of aldosterone in left ventricular hypertrophy (LVH) and geometry in patients with untreated essential hypertension (EHT), and investigated the contribution of myocardial fibrosis to the process of LVH.

Methods and Results The relationship of the plasma aldosterone concentration (PAC) to LVH and left ventricular (LV) geometry was investigated in 57 consecutive patients with untreated EHT. PAC correlated with both LV mass index (LVMI: r=0.46, p=0.0004) and relative wall thickness (RWT: r=0.33, p=0.013). In patients with LVH (LVMI ≥125 g/m²), the serum concentration of procollagen type III amino-terminal peptide (PIIINP), a marker of myocardial fibrosis, correlated with RWT (r=0.46, p=0.029). These patients were divided into 2 groups: concentric hypertrophy (CH) with RWT ≥0.44, and eccentric hypertrophy (EH) with RWT <0.44. The serum PIIINP concentration was significantly higher in the CH group than in the EH group (0.52±0.02 ng/ml vs 0.44±0.03 ng/ml, respectively; p<0.05).

Conclusions Aldosterone may be involved in LVH and LV geometry, particularly in the development of CH. Myocardial fibrosis seems more strongly involved in the hypertrophic geometry of CH than with EH. (Circ J 2007; 71: 716–721)

Key Words: Aldosterone; Essential hypertension; Left ventricular hypertrophy; Left ventricular geometry; Procollagen type III amino-terminal peptide

Left ventricular hypertrophy (LVH) represents an independent risk factor for cardiovascular mortality and morbidity in patients with hypertension (HT)1–2. In particular, concentric LVH is associated with a higher risk of cardiac arrhythmias, and even sudden death, and predicts the development of heart failure.3–5 Hemodynamic load is strongly involved in the development of LVH in HT, but blood pressure and the degree of LVH do not necessarily correlate. The development of LVH is influenced by various neurohumoral factors, and the renin-angiotensin-aldosterone system is strongly involved.6 Several reports have indicated the possibility that aldosterone directly promotes myocardial hypertrophy and interstitial fibrosis.7–11 A correlation between left ventricular (LV) myocardial mass and plasma aldosterone concentration (PAC) has already been reported in patients with essential HT (EHT). Some investigations have detailed LVH and the LV geometry in EHT patients already receiving treatment12–15 but there are no studies of patients with untreated EHT.

Accordingly, the role of aldosterone in LVH and the LV geometry in patients with untreated EHT remains unclear. In the present study we focused on the serum procollagen type III amino-terminal peptide (PIIINP), which is formed during the conversion of procollagen type III to collagen type III and released into the blood, then cleared from the blood via hepatobiliary elimination. The serum concentration of PIIINP has recently gained attention as reflecting ongoing fibrosis in the heart.16–24

The present study had the primary objective of elucidating the relationship between aldosterone and LVH and LV geometry in patients with untreated EHT. In addition, the degree of ongoing fibrosis associated with various geometrical patterns of LVH was examined by assaying the serum PIIINP concentrations. Finally, the contribution of myocardial fibrosis to the process of LVH is discussed.

Methods

Patients

We enrolled 57 consecutive patients (27 men, 30 women; mean age, 56±2 years) with untreated EHT. The criteria for HT were: systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg. Patients with the following diseases were excluded from the study: secondary HT, coronary artery disease, valvular heart disease, atrial fibr-
rillation, LV systolic dysfunction (LV ejection fraction (LVEF) ≤50%), or renal disorder (serum creatinine level ≥1.5 mg/dl). Conditions associated with elevated serum concentrations of PIIINP were likewise excluded (liver disease, bone disease, malignant disease, diabetes mellitus, pulmonary fibrosis or collagen disease). All patients gave written informed consent to participate in the study and the investigations conformed to the principles outlined in the Declaration of Helsinki.

Height, weight, blood pressure and heart rate were recorded for each patient. Blood pressure and heart rate were measured with the patient seated, after a 5-min rest period. Two measurements were obtained at 5-min intervals, then averaged. In addition, blood tests and echocardiography were performed within 2 weeks of the initial examination, while the patient was untreated.

**Biochemical Determinations**

Fasting blood samples were collected while the patient was supine and had rested for 20 min. Plasma renin activity (PRA) and PAC were measured using commercially available radioimmunoassay kits (PRA [SRL] kit, SRL, Tokyo, Japan; SPAC-S Aldosterone Kit, Dai-ichi Radio-isotope, Tokyo, Japan). Plasma brain natriuretic peptide (BNP) and serum PIIINP concentrations were also measured using commercially available immunoradiometric assay kits (Shionoria BNP Kit, Shionogi, Osaka, Japan; RIA-gnost PIIINP c.t., CIS Bio International, Saclay, France). Standard serum biochemistry tests were performed at the same time.

**Echocardiographic Measurement**

Comprehensive 2-dimensional echocardiography was performed using a Sonos-2500 echocardiograph (Philips, USA). Recordings were obtained at rest according to the recommendations of the American Society of Echocardiography. Measurements included LV dimension at diastole (LVDd), LV dimension at systole, interventricular septal thickness (IVST) and posterior wall thickness (PWT). LV mass was calculated in the parasternal long-axis view. LV mass was normalized for body surface area and expressed as the LV mass index (LVMI), which was calculated using Devereux’s formula: 26 (LVMI = 1.04 [(LVDd + IVST + PWT) / 2] – 13.6). An LVMI value greater than 125 g/m² was taken as indicating LVMH. The relative wall thickness (RWT) was calculated as PWT × 100/LVDd and a value of more than 0.44 was accepted as indicating an increase. 27

Patients were divided into 4 groups according to their LV geometry: 5 N group, normal LVMI and RWT; concentric remodeling (CR) group, CR indicated by normal LVMI and increased RWT; eccentric hypertrophy (EH) group, EH indicated by increased LVMI and normal RWT; and concentric hypertrophy (CH) group, CH indicated by increased LVMI and RWT. In addition, pulse Doppler echocardiography was used to assess LV diastolic function. Peak velocities of the early diastolic filling wave (E wave) and atrial filling (A wave) were recorded and the E-to-A ratio (E/A) was calculated. Deceleration time (DcT) of the E wave was then determined.

**Statistical Analysis**

Data are expressed as means ± SE. Relationships between variables were assessed using univariate linear regression analysis and Pearson’s correlation coefficient. The Mann-Whitney U-test was used to compare the mean values in 2 groups. One-way analysis of variance with subsequent Bonferroni test or Fisher’s multiple comparison test was used to evaluate the differences among more than 3 groups. Values of p<0.05 were considered statistically significant. Statistical analyses were performed using Statview software (version 5.0, SAS Institute, NC, USA) for Macintosh.

**Results**

In univariate linear regression analysis, LVMI displayed positive correlations with diastolic blood pressure (r=0.32, p=0.014), mean blood pressure (r=0.28, p=0.037) and PAC (r=0.46, p=0.0004), and RWT showed a positive correlation with PAC (r=0.33, p=0.013) (Table 1, Fig 1).

No significant differences in blood pressure or heart rate were identified for the 4 groups, but body mass index was significantly higher in the CR and CH groups than in the N group. Serum creatinine levels in the CH group were significantly higher in the CH group than in the N and CR group (Table 2). No significant differences between groups were found in

![Graph A](image1.png)  
**Fig 1.** (A) Relationship between LVMI and PAC. (B) Relationship between RWT and PAC. LVMI, left ventricular mass index; PAC, plasma aldosterone concentration; RWT, relative wall thickness.
relation to LVMI, as an index of systolic function, or E/A and DcT, as indices of LV diastolic function (Table 3). PAC (72±5 pg/ml vs 112±11 pg/ml, respectively; p<0.01) was significantly higher in the CH group than in the N group (Fig 2). Plasma BNP and PAC concentration did not differ significantly among the 4 groups.

When the EH and CH groups displaying LVH were evaluated, they showed no significant differences in relation to LVMI or plasma BNP concentrations. However, serum PIIINP concentration was significantly higher in the CH group than in the EH group (0.52±0.02 ng/ml vs 0.44±0.03 ng/ml, respectively; p<0.05). PAC and DcT values also tended to be higher in the CH group than in the EH group, but no significant differences were identified (Fig 3).

In addition, serum PIIINP concentration showed a significant correlation (r=0.46, p=0.029) with RWT in the combined LVH group (ie, EH+CH group) (Fig 4).

**Discussion**

This is apparently the first report to demonstrate that plasma or serum levels of aldosterone and PIIINP correlate with LVH and geometrical pattern in patients with untreated EHT. Studies have been conducted in patients treated using antihypertensive agents but drugs such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers may modify the development of LVH.

Increased aldosterone levels within the physiologic

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### Table 2 Clinical and Biochemical Characteristics

<table>
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<tr>
<th></th>
<th>N (n=28)</th>
<th>CR (n=6)</th>
<th>EH (n=9)</th>
<th>CH (n=14)</th>
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<tr>
<td>Age (years)</td>
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<td>60±1</td>
<td>54±2</td>
<td>53±3</td>
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<tr>
<td>M/F</td>
<td>12/16</td>
<td>0/6</td>
<td>4/5</td>
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<td>SBP (mmHg)</td>
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<td>DBP (mmHg)</td>
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<tr>
<td>MBP (mmHg)</td>
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<td>116±4</td>
<td>120±7</td>
<td>120±4</td>
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<tr>
<td>HR (beats/min)</td>
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<td>BMI (kg/m²)</td>
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<td>Cr (mg/dl)</td>
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<td>K (mmol/L)</td>
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*p<0.05 vs N, †p<0.05 vs CR, †† p<0.01 vs CR. N, normal left ventricle; CR, concentric remodeling; EH, eccentric hypertrophy; CH, concentric hypertrophy; HR, heart rate; BMI, body mass index; Cr, creatinine. Other abbreviations see in Table 1.

### Table 3 Echocardiographic Parameters

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<tr>
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<th>CR (n=6)</th>
<th>EH (n=9)</th>
<th>CH (n=14)</th>
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<td>8.6±0.2</td>
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<td>PWT (mm)</td>
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<td>LVDd (mm)</td>
<td>47.1±0.6</td>
<td>42.8±1.3*</td>
<td>52.9±1.2**†††</td>
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<td>LVMI (g/m²)</td>
<td>98.2±3.1</td>
<td>103.4±5.6</td>
<td>149.2±7.2*†††</td>
<td>159.0±6.5*†††</td>
</tr>
<tr>
<td>RWT</td>
<td>0.36±0.01</td>
<td>0.47±0.01**</td>
<td>0.38±0.01†††</td>
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<td>LVEF (%)</td>
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<td>74±1</td>
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<td>E/A</td>
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<tr>
<td>DcT (ms)</td>
<td>187±7</td>
<td>185±9</td>
<td>174±12</td>
<td>201±13</td>
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</table>

*p<0.05 vs N, **p<0.01 vs N, ††p<0.01 vs CR, †p<0.05 vs EH, #p<0.01 vs EH. IVST, intraventricular septal thickness; PWT, posterior wall thickness; LVDd, left ventricular dimension at diastole; LVMI, left ventricular mass index; RWT, relative wall thickness; LVEF, left ventricular ejection fraction; E/A, early/atrial transmitral Doppler flow velocity; DcT, deceleration time of early transmitral Doppler flow. Other abbreviations see in Table 2.

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Fig 2. Comparison of PRA (A), PAC (B) and plasma BNP levels (C) in the 4 study groups. *p<0.01 vs N group. N, normal left ventricle; CR, concentric remodeling; EH, eccentric hypertrophy; CH, concentric hypertrophy; PRA, plasma renin activity; PAC, plasma aldosterone concentration; BNP, brain natriuretic peptide.
Aldosterone and LV Geometry in EHT

The PAC of many patients in the present study was within the physiologic range and a major finding of the present study was the positive correlation between PAC and both LVMIs and RWT in all patients, particularly the significantly high PAC and PIIINP values in patients with CH. These findings indicate the possibility that plasma aldosterone, even within the physiologic range, is involved in the development of hypertensive cardiac hypertrophy and can cause increases in LV mass and concentric changes. However, we also consider that the action of this hormone should be evaluated by not only plasma level but also cardiac tissue levels, because aldosterone is produced in the myocardium of patients with HT.

There is a slight possibility of the clearance of each factor having been influenced by the difference in serum creatinine levels, even within the normal limits, in each group. However, PIIINP in particular is reportedly cleared from the blood via hepatobiliary elimination and does not depend on renal function.

Several reports have suggested the possibility that aldosterone not only indirectly causes LVH by increasing circulating plasma volume and elevating blood pressure, but also directly promotes myocardial hypertrophy and interstitial fibrosis. Weber et al used a hypertensive rat model and showed that aldosterone administration increased both blood pressure and interstitial and perivascular fibrosis, while coadministration of spironolactone, an aldosterone receptor antagonist, completely inhibited the development of fibrosis even at dosages that did not demonstrate an antihypertensive effect. In addition, aldosterone has been shown to increase extracellular matrix and collagen deposition in the myocardium by enhancing the expression of cardiac collagen type I and III genes.

Various other investigations have reported correlations between the LVMIs and PAC in patients with HT. However, results regarding the relationships between LVH and geometric pattern and PAC have been inconsistent. Iwashima et al and Muscholl et al postulated that PAC was highest in the patient group showing EH, because the increase in circulating plasma volume caused by aldosterone leads to eccentric changes; however, patients who were being administered antihypertensive agents were included in their studies. Conversely, Shigematsu et al and Soylu et al reported that values for PRA and PAC were highest in the CH patient group. Tanabe et al reported that CH was the most common LV geometric pattern in patients with primary aldosteronism, indicating that a high PAC leads to the development of CH.

PIIINP is released into the blood at the time of collagen synthesis, and has recently gained attention as a marker of ongoing tissue fibrosis in the cardiovascular organs. Matoba et al administered delapril hydrochloride, an ACE inhibitor, for 12 months to hypertensive patients with accompanying LVH and reported that serum PIIINP concentrations and LV mass were both reduced by this treatment. Sato et al added spironolactone to an ACE inhibitor as drug therapy for EHT patients, and found that this combination significantly reduced both LVMIs and the serum PIIINP concentration. In addition, Tsutamoto et al per-
formed cardiac catheterization to collect blood from the coronary sinus and aorta in chronic heart failure patients, which showed that the index of aldosterone incorporation into the heart correlated positively with LV end-diastolic volume and serum PIIINP concentration. Moreover, the Randomized Aldactone Evaluation Study (RALES) showed that the outcome in patients with severe chronic heart failure was strikingly improved when spironolactone was added to the treatment regimen. Zannad et al. performed subanalysis of the RALES results and demonstrated that 6 months' administration of spironolactone brought about a significant decrease in serum PIIINP concentration compared with placebo, that outcome was better in the low-PIIINP-concentration group compared with the high-concentration group. These reports suggest that aldosterone may be directly incorporated into cardiac tissue and is strongly involved in the development of remodeling of the LV.

In order to avoid the influence of fibrosis of organs other than the heart, the serum PIIINP levels were examined among the groups with LVH. The present study found that the serum PIIINP concentration was significantly correlated with RWT in the combined LVH group (ie, EH+CH group). Moreover, despite the fact that the E and CH groups showed no differences in relation to LVMI or BNP, the serum PIIINP concentration was significantly higher in the CH group than in the EH group. Values for PRA and PAC also tended to be higher in the CH group than in the EH group, but no significant differences were identified. These findings suggest that the development of interstitial fibrosis is more strongly involved in CH than in EH, and that aldosterone likely influences the development of fibrosis.

Taniuchi et al. recently reported that the addition of spironolactone significantly reduced LVMI only in the concentric LV hypertrophy subgroup of hypertensive patients receiving angiotensin II receptor blocker treatment. That result strongly supports our data showing that CH is influenced by aldosterone.

The processes underlying the changes in the LV geometry that occur during hypertensive cardiac hypertrophy have yet to be elucidated. Animal studies have shown that aldosterone causes fibrosis of the myocardium and impairs LV diastolic function, and correlations between PAC and impaired LV diastolic function have been described in EHT patients. Considering these findings together with the present results leads to the following concepts. If the aldosterone-induced myocardial fibrosis progresses, impaired LV diastolic function and CH appear. In such patients, activation of aldosterone receptors in the heart may be strongly potentiated, or aldosterone production in myocardial tissue may be accelerated. Further progression of myocardial fibrosis would gradually lead to impaired LV systolic function, followed by enlargement of the LV chamber, a decrease in the movement of the LV wall, and development of a state of hypertensive heart failure. However, our present results showed no association between PAC and diastolic LV filling velocities, including the E/A ratio, as was found in a previous report.

According to the observational study of 32 untreated EHT patients by Conrado et al. during a 5-year period, among the 8 patients who initially showed normal LV geometry 4 developed CH, 3 others progressed to EH, and the remaining case was unchanged. The 2 cases that initially showed CR both developed into CH. There was no case of a change from CH to EH or from EH to CH. Moreover, they was described that in the majority of cases the remodeling pattern remained unchanged and that the LVMI increased or decreased within that pattern. Their observations and our data together lead to the following speculation. In HT patients with an eccentric pattern, enlargement of the LV is caused mainly by hemodynamic load, and the degree of fibrosis of myocardial cells is milder than the degree of hypertrophy, the LV myocardium is stretched, the LV chamber is expanded, and the pattern is that of EH. On the other hand, a subgroup strongly influenced by aldosterone displays more advanced myocardial fibrosis, and develops a CR pattern.

The present study showed that the PIIINP levels in the N and CR groups tended to be higher than in the EH group. Because serum PIIINP levels do not express the amount of fibrosis but rather the ongoing rate of fibrosis in tissue, we therefore speculated that the group included some patients in the N or CR group in whom myocardial fibrosis was progressing quickly and who would change to CH in the near future.

A previous report showed that the group of patients presenting with CH has the worst prognosis. It appears to be very important in the treatment of HT to block aldosterone in order to prevent the development of CH.

In conclusion, our observations indicate that aldosterone is associated with a concentric pattern of LV geometry in patients with untreated EHT. For patients with untreated EHT, the blood concentration of PAC and serum PIIINP are useful for assessing the status of LVH. Further investigations are needed to evaluate whether aldosterone blockade will improve the geometry of the LV of the hypertensive heart.

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References
5. Koren MJ, Devereux RB, Casale PN, Savage DD, LaRagh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med 1991; 114: 345–352.
11. Brilla CG, Matsubara LS, Weber KT. Antiﬁbrotic effects of spironolactone in preventing myocardial fibrosis in systemic arterial hyper-


