Asymmetric Ventricular Hypertrophy in Patients with Essential Hypertension

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SUMMARY

We attempted to clarify the pathogenesis of asymmetric ventricular hypertrophy in hypertensive patients, especially regarding sympathetic nervous system and renin-angiotensin system. Subjects were divided in 3 groups by echocardiographic findings; 1) 15 patients with non-hypertrophy (NH), 2) 14 patients with symmetric hypertrophy (SH), and 3) 10 patients with asymmetric hypertrophy (ASH).

Subjects with ASH showed following features. Age (53.7±1.6 yr) was older than NH (43.7±1.4 yr) but not different from SH (49.7±2.3 yr). Mean arterial pressure (119.0±3.9 mmHg) was higher than NH (107.5±1.4 mmHg) but not different from SH (122.4±2.8 mmHg). End-diastolic and end-systolic dimensions were smaller and ejection fraction was larger than those of NH and SH. Cardiac index (3.90±0.37 L/min/M²) was largest among 3 groups. UNE (19.5±3.5 μg/day) was lower than SH (31.2±2.5 μg/day). PRA (0.44±0.16 ng/ml/h) was lower than SH (1.53±0.20 ng/ml/h) and NH (1.62±0.28 ng/ml/h). Ejection fraction was correlated with UNE (r=0.835) and PRA (r=0.736).

We suggest that the heart of hypertensives with ASH is in hyperdynamic state due to the hyperresponsiveness to sympathetic stimuli, although they have a decrease of sympathetic nervous activity, and the renin-volume axis may have no important role on the pathogenesis of ASH.

Additional Indexing Words:
Essential hypertension  Asymmetric ventricular hypertrophy  Norepinephrine  Plasma renin activity

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ECHOCARDIOGRAPHY has introduced a new dimension in the study of hypertensive heart disease. Several investigators have reported the occurrence of asymmetric ventricular hypertrophy among hypertensive patients in various prevalence. However, the difference in pathogenesis between symmetric ventricular hypertrophy, which is commonly seen in hypertensive disease, and asymmetric ventricular hypertrophy is not clear yet.

It is generally viewed that the most important cause of left ventricular hypertrophy in hypertensive patients might be the pressure load imposed on the myocardium. In addition, it is also considered recently that other factors such as genetic predisposition, neurohumoral factors, altered myocardial composition and so on could play participating role in determining the degree of ventricular hypertrophy.

In this study we attempted to elucidate the pathogenesis of asymmetric ventricular hypertrophy in essential hypertension, especially to clarify the role of sympathetic nervous system and renin-angiotensin system. We evaluated echocardiographic dimensions, systolic time interval, hemodynamic measurements, and clinical characteristics including urinary excretion of catecholamines, plasma renin activity, and plasma aldosterone concentration in hypertensive patients with asymmetric hypertrophy as compared with those of hypertensives with symmetric hypertrophy or without ventricular hypertrophy.

SUBJECTS

The study group included 39 patients with essential hypertension of mild to moderate degree. All patients were either untreated or had been discontinued therapy at least 3 weeks before the study. All subjects were hospitalized and placed on a diet of 167 mEq/day of sodium. Investigations included intravenous pyelography, renography, determinations of serum creatinine and electrolyte levels, urinary excretion of catecholamines, plasma renin activity, plasma aldosterone concentration, and renal clearance ($C_{PAH}$ and $C_{Thio}$).

All subjects were diagnosed as having essential hypertension. The following patients were not included: 1) patients with malignant hypertension, 2) patients with malignant hypertensive retinopathy (i.e. Keith-Wagener Classification III or IV), 3) patients with a history of angina pectoris, myocardial infarction or congestive heart failure, and 4) patients with marked reduction of renal function.

Patients were divided into 3 groups according to echocardiographic findings.

Group of non-hypertrophy (NH): Fifteen patients had normal left ven-
tricular echogram without any findings described below.

Group of symmetric hypertrophy (SH): Fourteen patients showed symmetric hypertrophy of the left ventricle defined by the summed thickness of the interventricular septum and the posterior left ventricular wall (IVS+PW) ≥2.6 cm, and a ratio of the thickness of the septum to the posterior wall (IVS/PW) ≤1.3.

Group of asymmetric hypertrophy (ASH): Ten patients demonstrated asymmetric septal hypertrophy characterized by IVS≥1.5 cm, and IVS/PW >1.3.

METHODS

Echocardiography: The methods of recording of echocardiograms were described in detail elsewhere. In brief, they were recorded using IREX system II ultrasonoscope and a 2.25 MHz transducer (ø 13 mm). The left ventricular diameter at end-diastole (LVDd) was measured at the peak of R wave of the simultaneously recorded electrocardiogram. The left ventricular diameter at end-systole (LVDs) was taken at the point where the posterior left ventricular wall and the interventricular septum converged each other maximally. Echocardiographic ejection fraction (EF) was calculated as following; EF=(LVDd³−LVDs³)/LVDd³. The thickness of the posterior left ventricular wall (PW) and the interventricular septum (IVS) was measured just before atrial systole.

Hemodynamic measurements and systolic time intervals: On the 7 to 10th day of the patient’s hospitalization, hemodynamic and biochemical studies were performed. Blood pressure was measured in the supine position with standard sphygmomanometric method. Mean arterial pressure was estimated from the sum of the diastolic pressure and one-third of the pulse pressure. Cardiac output was determined in duplicate with the dye-dilution method using ear-piece (Nihon-Koden, cardiac output computer MLC-4100).

Systolic time interval (STI) was measured by the simultaneous recording of indirect carotid artery pulse tracing, external phonocardiogram and electrocardiogram at a paper speed of 100 mm/sec. Pre-ejection period (PEP) and left ventricular ejection time (LVET) were corrected for heart rate. The ratio of pre-ejection period to left ventricular ejection time (PEP/LVET) was also evaluated.

Plasma renin activity (PRA) and plasma aldosterone concentration (PAC): Blood samples for determination of PRA and PAC were taken on the early morning of the day of hemodynamic study (6:00 AM) with the patients in the supine position. PRA and PAC were determined by radio-
immunoassay using renin activity assay kits (CIS and Midorijuji) and aldosterone assay kits (Aldosterone-Riakit, Dinabot), respectively.

Plasma volume (PV): PV was determined on the same day of PRA measurement using $^{131}$I-HSA.

Urinary excretion of catecholamines: Urinary excretion of norepinephrine ($U_{NE}$) and epinephrine ($U_E$) were determined for 3 successive days just before hemodynamic study. Catecholamines were determined by trihydroxyindol (THI) method using fluid chromatography.

Renal blood flow and glomerular filtration rate: Renal blood flow was determined by PAH-clearance and hematocrit. Glomerular filtration rate was determined by sodium thiosulfate clearance. Both were determined by single injection method, and were corrected to the standard body surface area (1.48 M$^2$).

Results were recorded as means±standard errors of the means (means±SEM). The differences in all parameters among NH, SH, and AHS were statistically analyzed by Student’s t-test. Results were referred to as significant when their p values were <0.05.

RESULTS

Echocardiographic dimensions (Table I, Figs. 1 and 2): In subjects with ASH, end-diastolic dimension was smaller than that of NH, end-systolic dimension was smaller than those of NH and SH, and ejection fraction was larger than those of NH and SH (Table I).

Ejection fraction in patients with ASH was significantly correlated with $U_{NE}$ (Fig. 1) and with PRA (Fig. 2). In patients with NH and SH, these

<table>
<thead>
<tr>
<th></th>
<th>NH (n=15)</th>
<th>SH (n=14)</th>
<th>ASH (n=10)</th>
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</thead>
<tbody>
<tr>
<td>Interventricular septal (IVS) thickness (cm)</td>
<td>1.02±0.02</td>
<td>1.42±0.05</td>
<td>2.02±0.08</td>
</tr>
<tr>
<td>Posterior wall (PW) thickness (cm)</td>
<td>0.98±0.03</td>
<td>1.38±0.04</td>
<td>1.20±0.06</td>
</tr>
<tr>
<td>IVS/PW</td>
<td>1.06±0.04</td>
<td>1.05±0.03</td>
<td>1.73±0.12</td>
</tr>
<tr>
<td>End-diastolic dimension (cm)</td>
<td>4.74±0.10</td>
<td>4.43±0.14</td>
<td>4.15±0.18</td>
</tr>
<tr>
<td>End-systolic dimension (cm)</td>
<td>2.91±0.09</td>
<td>2.85±0.11</td>
<td>2.28±0.11</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.73±0.02</td>
<td>0.72±0.02</td>
<td>0.83±0.01</td>
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</tbody>
</table>

Values are mean±SEM.

* p<0.05, ** p<0.01, *** p<0.005, **** p<0.001.
ASYMMETRIC HYPERTROPHY IN HYPERTENSION

Fig. 1 (left). The relationship between urinary excretion of norepinephrine (UNE) and echocardiographic ejection fraction (EF) in hypertensives with asymmetric ventricular hypertrophy.

Fig. 2 (right). The relationship between plasma renin activity (PRA) and echocardiographic ejection fraction (EF) in hypertensives with asymmetric ventricular hypertrophy.

Table II. Hemodynamic Measurements and Systolic Time Intervals

<table>
<thead>
<tr>
<th></th>
<th>NH (n=15)</th>
<th>SH (n=14)</th>
<th>ASH (n=10)</th>
<th>NH vs SH</th>
<th>NH vs ASH</th>
<th>SH vs ASH</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAP (mmHg)</td>
<td>136.3±2.8</td>
<td>163.1±5.5</td>
<td>164.2±8.2</td>
<td>****</td>
<td>***</td>
<td>NS</td>
</tr>
<tr>
<td>DAP (mmHg)</td>
<td>93.1±1.4</td>
<td>102.0±2.4</td>
<td>96.2±2.7</td>
<td>***</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>107.5±1.4</td>
<td>122.4±2.8</td>
<td>119.0±3.9</td>
<td>****</td>
<td>**</td>
<td>NS</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>3.09±0.25</td>
<td>2.78±0.19</td>
<td>3.90±0.37</td>
<td>NS</td>
<td>NS</td>
<td>*</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>66.9±2.7</td>
<td>62.3±2.9</td>
<td>58.9±3.6</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PEPc (msec)</td>
<td>146.4±4.0</td>
<td>157.4±0.2</td>
<td>156.0±3.8</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>LVETc (msec)</td>
<td>371.5±3.1</td>
<td>360.8±4.0</td>
<td>371.8±5.3</td>
<td>*</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PEP/LVET</td>
<td>0.395±0.011</td>
<td>0.438±0.014</td>
<td>0.421±0.013</td>
<td>*</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SEM.
* p<0.05, ** p<0.01, *** p<0.005, **** p<0.001.

SAP=systolic arterial pressure; DAP=diastolic arterial pressure; MAP=mean arterial pressure; CI=cardiac index; HR=heart rate; PEPc=corrected pre-ejection period; LVETc=corrected left ventricular ejection time.

correlations were not observed.

Hemodynamic measurements and STI (Table II): Seven out of 15 patients with NH, 1 out of 14 patients with SH, and 2 out of 10 patients with ASH were labile hypertension; namely their blood pressure was sometimes normotensive (less than 140/90 mmHg) during the hospitalization of first 7 to 10 days. Other patients were all sustained hypertension; i.e. their blood pressure was always above 140/90 mmHg.
Systolic and mean arterial pressures of ASH were significantly higher than those of NH, but were not different from those of SH. Diastolic arterial pressure of ASH was not statistically different from that of NH.

Cardiac index of patients with ASH was largest among 3 groups and the difference between that of ASH and SH was statistically significant.

Heart rate and PEPc were not different among 3 groups.

Table III. Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>NH  (n=15)</th>
<th>SH  (n=14)</th>
<th>ASH (n=10)</th>
<th>NH vs SH</th>
<th>NH vs ASH</th>
<th>SH vs ASH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr.)</td>
<td>43.7±1.4</td>
<td>49.7±2.3</td>
<td>53.7±1.6</td>
<td>NS</td>
<td>****</td>
<td>NS</td>
</tr>
<tr>
<td>PRA (ng/ml/h)</td>
<td>1.62±0.28</td>
<td>1.53±0.20</td>
<td>0.44±0.16</td>
<td>NS</td>
<td>***</td>
<td>****</td>
</tr>
<tr>
<td>PAC (pg/ml)</td>
<td>42.3±9.8</td>
<td>61.1±13.5</td>
<td>28.6±4.2</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PV (ml/Kg)</td>
<td>49.8±2.6</td>
<td>49.2±2.4</td>
<td>49.6±2.8</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>UNE (µg/day)</td>
<td>27.4±2.3</td>
<td>31.2±2.5</td>
<td>19.5±3.5</td>
<td>NS</td>
<td>NS</td>
<td>*</td>
</tr>
<tr>
<td>UE (µg/day)</td>
<td>5.9±0.8</td>
<td>6.1±1.1</td>
<td>5.7±1.1</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>RBF (ml/min)</td>
<td>639.3±40.7</td>
<td>474.3±42.2</td>
<td>515.0±58.2</td>
<td>*</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>94.6±6.4</td>
<td>71.3±7.0</td>
<td>80.0±2.8</td>
<td>*</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

* p<0.05, *** p<0.005, **** p<0.001.

PRA=plasma renin activity; PAC=plasma aldosterone concentration; PV=plasma volume; UNE=urinary norepinephrine excretion; UE=urinary epinephrine excretion; RBF=renal blood flow; GFR=glomerular filtration rate.

Fig. 3 (left). Plasma renin activity (PRA) in hypertensives with no ventricular hypertrophy (NH), symmetric ventricular hypertrophy (SH), and asymmetric ventricular hypertrophy (ASH).

Fig. 4 (right). Urinary excretion of norepinephrine (UNE) in hypertensives with no ventricular hypertrophy (NH), symmetric ventricular hypertrophy (SH), and asymmetric ventricular hypertrophy (ASH).
Fig. 5. The relationship between plasma renin activity (PRA) and urinary excretion of norepinephrine (UNE) in hypertensives with asymmetric ventricular hypertrophy.

In patients with SH, LVETc was shortest and PEP/LVET was largest among 3 groups. These were not statistically different between ASH and NH.

Clinical characteristics (Table III, Figs. 3, 4, and 5): Age of patients was 29 to 54 years old (average 43.7±1.4) in NH group, 32 to 56 years old (average 49.7±2.3) in SH group, and 45 to 64 years old (average 53.7±1.6) in ASH group. ASH group was significantly older than NH group, but not statistically different from SH group.

PRA of ASH group was significantly lower than either that of NH or that of SH (Fig. 3). UNE was also reduced in patients with ASH. It was significantly different between ASH and SH, but not between ASH and NH (Fig. 4). PRA was significantly correlated with UNE in ASH group (Fig. 5). But this relationship was not observed in NH or SH group.

PAC, PV, and UE were not statistically different among 3 groups.

Renal blood flow and glomerular filtration rate were lowest in patients with SH. Those of ASH were intermediate between those of NH and SH.

**Discussion**

In this study, average age of patients with ASH and SH was not statistically different, but was significantly older than patients with NH. Both patients with ASH and SH were mostly observed among sustained hypertensives. Average mean arterial pressure of these groups was significantly higher than that of NH groups. In patients with NH, labile hypertension was more frequently observed. These suggest an important role of the level of blood pressure and duration of hypertension or aging itself on the cardiac hypertrophy.
On the other hand, Safar et al\textsuperscript{7} reported that ASH was frequently observed among patients with borderline hypertension, and was rare in patients with sustained hypertension. It seems that their results were not in agreement with ours. However, their subjects were much younger than ours; i.e. average age was 27.2±1.2 years old in patients with borderline hypertension and 32.7±4.1 years old in patients with sustained hypertension. Although previous reports other than Safar et al had not indicated whether subjects were with borderline or sustained hypertension, it was clear from the data that many patients with ASH were under sustained hypertension.\textsuperscript{11,12} Therefore it is likely that ASH is not uncommon in patients with either borderline hypertension in younger age group or sustained hypertension.

Shortened LVETc and larger PEP/LVET in patients with SH suggested a deterioration of the cardiac function compared to patients with NH. Renal function was also deteriorated in patients with SH compared to patients with NH. These were not statistically different between patients with ASH and NH, suggesting that the cardiovascular and renal complications in patients with ASH were mild compared to patients with SH. Genda et al\textsuperscript{12} could not show any difference in clinical characteristics including ejection fraction and end-diastolic volume revealed by angiographic studies, renal function, and ophthalmoscopic findings between patients with ASH and SH. Our results were not in accordance with them, but again confirmed previous results.\textsuperscript{2}

Characteristic echocardiographic findings of patients with ASH in our study were significantly increased ejection fraction and reduced end-systolic dimension as well as increased interventricular septal/posterior wall ratio as compared to patients with SH or NH. Cardiac index was also larger in patients with ASH than in patients with SH. These indicate hyperdynamic state of the heart in patients with ASH. In connection with these results, the suggestion of Safar et al\textsuperscript{7} is worth notice. They suggested that an increased adrenergic activity might have some role on the increased interventricular septal/posterior wall thickness ratio in borderline hypertension. In this regard, it was unexpected findings that urinary excretion of norepinephrine was reduced in patients with ASH in our study. Although levels of urinary excretion of norepinephrine is just a rough index of sympathetic nervous activity, it seems that hypertensives with ASH are rather depressive state of sympathetic nervous system or at least not augmented adrenergic state. It is seemingly a difficult problem to conciliate the results of ours and those of Safar et al.\textsuperscript{7} It is well known that patients with borderline hypertension and hyperkinetic circulation simultaneously have an increase of sympathetic and a decrease of parasympathetic activity.\textsuperscript{13} However, it is not known whether sympathetic nervous activity is similar or not between patients with ASH and
those with SH or NH in borderline hypertension. It will be useful to study on this issue to clarify the pathogenesis of ASH in borderline hypertensives.

The cause of hypertensive cardiac hypertrophy has often been simply viewed as mechanical factor; i.e. pressure overload to the myocardium. However, recent studies suggested the implication of various neurohumoral factors and renin-angiotensin system. In our study, PRA was not different between NH and SH, but was significantly reduced in ASH compared with NH and SH. PAC also tended to be low in ASH, but was not achieved statistical significance. Since PV was not different among 3 groups and diet was same, reduced PRA in ASH might be caused by reduced activity of sympathetic nervous system. This was supported by the fact that PRA was correlated with U_NE in patients with ASH (Fig. 5). In other words, reduced PRA might have no primary role for the pathogenesis of ASH in hypertensive disease. Rather it might be a secondary effect of reduced activity of sympathetic nervous system. PV was not different among 3 groups. Therefore, renin-volume axis which has been viewed as an important factor in regulation of blood pressure, and possibly in state of vascular complication of hypertensive disease may not be implicated in the pathogenesis of ASH in hypertensive disease.

Although ASH in hypertensives seems to be in the state of reduced sympathetic nervous activity, their heart was in the hyperdynamic state. This is probably not the secondary changes in sympathetic receptors of the heart due to reduction of the sympathetic drive, because patients in group NH and SH who showed low excretion of norepinephrine or PRA were not accompanied by hyperdynamic state of the heart. Furthermore, ejection fraction of ASH was significantly correlated with U_NE (Fig. 1), and PRA (Fig. 2). These relations were not observed in patients with NH and SH. Therefore, it is possible that the heart of the patients with ASH is particularly sensitive to the sympathetic stimuli.

We speculate that the myocardium of ASH might be hyperresponder to circulating catecholamines for some reasons including possibly genetic predisposition. Hyperresponsive heart easily augment cardiac output and blood pressure by the stimuli of catecholamine release. Then, baroreceptors in arterial system exerts a modulating action on the sympathetic nervous system, resulting in reduced activity. Therefore, urinary excretion of norepinephrine and PRA in patients with ASH are reduced at rest. If it is so, it is possible that ASH is not necessarily a complication of hypertension, but sometimes plays an active role or at least an additive role in initiation or augmentation of hypertension when sympathetic nervous system is activated for some reasons. To verify this assumption, further studies are needed.
REFERENCES