Characteristics of Cardiovascular Morphology and Function in the High-Normal Subset of Hypertension Defined by JNC-VI Recommendations

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A cross-sectional study was conducted to compare the morphological and functional characteristics of the cardiovascular system among subgroups of hypertension defined by the JNC-VI recommendations. One hundred and sixteen subjects (normotensives and unmedicated hypertensives: 49 ± 10 yr) were classified into 4 groups based on the criteria of JNC-VI: normotensive (NOR: n = 38), high-normal blood pressure (HN: n = 16), stage 1 hypertensive (SI: n = 28), and stage 2 to 3 hypertensive (SII-IIII: n = 34). Ultrasonographic examinations of the heart and carotid artery were performed in all subjects, and the following parameters were obtained: left ventricular mass index (LVMI), relative wall thickness at end-diastole (RWTd), cardiac diastolic function (A/E), common carotid artery diameter (CAD), intimal media thickness of the common carotid artery (IMT), and distensibility of the common carotid artery (Distens). RWTd, A/E, and IMT in SI (RWTd, 0.41 ± 0.07; A/E, 1.21 ± 0.41; IMT, 0.69 ± 0.17 mm) and SII-IIII patients (0.33 ± 0.03, 0.86 ± 0.21, 0.56 ± 0.10 mm) were larger than those in NOR patients (0.35 ± 0.09, 0.89 ± 0.20, 0.67 ± 0.15 mm) (p < .01). Furthermore, LVMI in SII-IIII (135.5 ± 35.5 g/m²) patients was larger than that in NOR patients (99.4 ± 17.5 g/m²) (p < .05). RWTd in HN patients (0.37 ± 0.06) was significantly higher than that in NOR patients (p < .01). A/E tended to be larger in HN than in NOR patients (p < 0.1). In the normotensives, no significant difference in any of the parameters was detected between those with optimal (n = 19) and normal (n = 19) blood pressure. Thus, both morphological and functional changes were associated with elevation of blood pressure. Cardiac morphological adaptation and functional impairment were present even in subjects with high-normal blood pressure level, while there were no significant differences between the normal and optimal subsets.

Key Words: hypertension, optimal blood pressure, high-normal blood pressure, relative wall thickness, cardiac diastolic function.

Hypertensive patients have morphologic changes of the heart, characterized by increased left ventricular (LV) wall thickness to compensate for increased stress on the LV walls (1). Moreover, persistent long-term hypertension may result in dilatation of the left ventricle, dilatation and/or elongation of arteries and arterioles, impairment of systolic and diastolic function of the left ventricle, and/or decrease in distensibility of arteries and arterioles (2), leading to cardiovascular end-organ damages (3).

The severity of hypertension is stratified according to the degree and the presence or absence of end-organ damage (4), although a classification of hypertension based on blood pressure level alone is also in wide use. The 6th report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI) classifies blood pressure in non-hypertensives as optimal, normal, or high-normal; and hypertension as mild (stage 1), moderate (stage 2), or severe (stage 3) (5). To prevent end-organ damage, it is worthwhile to investigate whether compensatory and non-compensatory changes in the cardiovascular system due to hypertension occur in relation to each of the stages of hypertension defined above.

In the present study, we studied the morphologic and functional characteristics of the heart and carotid artery by ultrasonography, in order to clarify the compensatory and non-compensatory changes in the cardiovascular system in normotensives and hypertensives classified according to the JNC-VI, with a particular focus on optimal and high-normal subsets.
Materials and Methods

Subjects
One hundred and sixteen subjects (76 men and 40 women, average age 49 ± 10 yr) with normal or high blood pressure who visited the Outpatient Clinic of the Division of Cardiology of Ichihara Hospital at the Teikyo University School of Medicine from June 1995 to February 1998, and whose echocardiograms were acceptable for measurements were enrolled in this study. None of the patients had a history of taking antihypertensive medication. Among the 116 subjects, 74 (48 men and 26 women) visited our clinic for management of hypertension and 42 (28 men and 14 women) visited annual health appraisals. Patients with secondary hypertension or other serious medical problems requiring specific treatment were excluded from the study. Based on the JNC-VI classification of hypertension (5), patients were divided into four groups: optimal or normal (normotensive; NOR); high-normal (HN); stage I (mild hypertension; SI); and stages 2 or 3 (moderate to severe hypertension; SII-III). The protocol of this study was approved by the Ethical Committee of Teikyo University Ichihara Hospital.

Blood Pressure Measurement
Blood pressure was measured in an office setting by the conventional cuff method with a mercury manometer. The blood pressure was recorded as the Korotkoff sound. As part of the evaluation of the distension of the common carotid artery, we also measured the blood pressure with the patient in a supine position immediately after the ultrasound examination.

Ultrasonographic Examinations
Ultrasonographic examination of the carotid artery, and M-mode and pulsed-Doppler two-dimensional echocardiograms were obtained with the subject in the left lateral decubitus position, using a Sonolayer (SSH-160A; Toshiba, Tokyo, Japan) equipped with a 2.5 MHz or 3.75 MHz transducer. Data were printed on a split-chart recorder at a speed of 50 mm/s. End-diastolic interventricular septal thickness (IVSTd), posterior wall thickness (PWTd), end-diastolic LV internal diameter (LVDd), end-systolic posterior wall thickness (PWTs), and end-systolic LV internal diameter (LVDs) were obtained according to the recommendations of The American Society of Echocardiography and the Penn Convention (6, 7). The dimensions presented were the means of two M-mode measurements made by two different investigators. The left ventricular mass (LVM), relative wall thickness at end-diastole (RWTd), cardiac output (CO), and end-systolic wall stress (ESS) were calculated according to the following formulae:
1) LVM = 1.04 × [(LVDd + PWTd + IVSTd)3 - LVDd3] - 13.6
2) RWTd = 2 × PWTd/LVDd
3) CO = (end-diastolic volume - end-systolic volume) × heart rate
4) ESS = (0.334 × SBP × LVDs)/PWTs [1 + (PWTs/LVDs)]

where SBP is the systolic blood pressure measured during ultrasonographic examination (8).

The LVM index (LVMI) and CO index (CI) were calculated by dividing the LVM and CO, respectively, by the body surface area (BSA). The peak early diastolic velocity (E) and peak atrial systolic velocity (A) were measured by pulsed-Doppler echocardiography; the A/E ratio was determined as a parameter of LV diastolic function (9).

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Long- and short-axis views of the common carotid artery, the carotid sinus, and the extracranial internal and external carotid arteries were obtained by ultrasonography (7.5 MHz transducer) while the subjects rested supine with the neck slightly extended. Two-dimensional longitudinal M-mode tracings were obtained approximately 1 cm proximal to the carotid sinus, and an electrocardiogram was recorded simultaneously. The presence of atheromatous plaque was defined as a relative thickening of the wall by 50% compared with the intact surrounding wall. Plaque was measured on B-mode images, with the plaque score determined according to a previously described method (10). If a plaque was detected in the area of interest, the probe was shifted toward the proximal portion of the common carotid artery where vascular function could be examined. The end-diastolic far wall thickness, and the end-diastolic and peak systolic internal dimensions (Dd and Ds, respectively), were the mean measurements of the M-mode images of the right and the left common carotid arteries obtained during three cardiac cycles. Carotid artery distensibility (Distens) was calculated using the following formula (11):

\[
\text{Distens (\% kPa)} = 100 \times \frac{(D_d^2 - D_d^2)}{D_d^2 - (BP - DBP)}
\]

(1 kPa = 7.6 mmHg), where SBP and DBP are the systolic and diastolic blood pressures, respectively, measured during ultrasonographic examination.

All measurements presented are the means of the results obtained by 2 observers. The reproducibility of the echocardiographic parameters in our institute has already been reported elsewhere (12, 13). The interobserver variability of the ultrasonographic measurements of the diameter of the carotid artery obtained in 20 volunteers was 2.2 ± 1.0%.

Laboratory Measurements
Plasma triglycerides, total cholesterol, high-density lipoprotein cholesterol, and blood sugar levels were measured enzymatically with a Hitachi 731 Analyzer (Hitachi, Tokyo, Japan). All blood samples were obtained in a fasting state in the early morning.

Statistical Analysis
Data are expressed as mean ± SD. Analysis of variance (Bonferroni’s method) was used to assess the difference between groups. P level of <.05 was
accepted as indicating statistical significance. Linear regression analysis and step-wised multiple regression analysis were performed to determine the equation variables for cardiovascular morphological and functional abnormalities. Statistical analyses were performed using the SPSS software package (SPSS, Chicago, IL).

Results

Table 1 shows the clinical characteristics of each group. There were no significant differences among the four groups except for blood pressures. Table 2 shows the results of the ultrasound examination of the heart and carotid artery in each group. RWTd, A/E and IMT in the SI and SII–III groups were larger than those in the NOR group. IMT in the SII–III group was also larger than in the HN group. LVMI and CAD in the SII–III group were also larger than those in the NOR and HN groups. Conversely, Distens was smaller in the SI and SII–III groups than in the NOR and HN groups (p < .01). CAD was larger in the SII–III group than in the NOR and HN groups (p < .01). In the normotensive group, no significant differences in clinical variables or cardiovascular functional and morphological variables were detected between the optimal and normal blood pressure groups (data not shown). Table 3 depicts correlation coefficients obtained from linear regression analyses between clinical variables and cardiovascular morphological and functional abnormalities. In the multiple regression analysis (Table 4), age was an equation variable for A/E and IMT; systolic blood pressure was an equation variable for RWTd, A/E, IMT and Distens; diastolic blood pressure was an equation variable only for LVMI; and plasma triglyceride level was also an equation variables for IMT. However, plasma level of total cholesterol, fasting blood glucose level, and body mass index were not equation variables for any cardiovascular parameters measured.

Discussion

Both the JNC-VI and 1999 WHO/ISH guidelines for management of hypertension recommend that
patients with high-normal blood pressure who have complications such as end-organ damage or other risk factors for arteriosclerosis are to be treated with life-style modification and drug therapy (5, 14). Recently, Nakanishi et al. reported that high-normal blood pressure is the strongest predictor of the development of hypertension among middle-aged Japanese men (15). To date, however, no study has evaluated the pathophysiological characteristics of the high-normal group. High blood pressure increases left ventricular wall stress. To compensate this increased stress, concentric morphological changes characterized by decreased left ventricular chamber and increased left ventricular wall thickness occur (1). The left ventricular response to the increased afterload causes not only myocardial cell hypertrophy, but also an increase in the number of interstitial components (1). As a result, impairment of left ventricular diastolic function can occur early in hypertension in the absence of remarkable left ventricular hypertrophy (17). In the present study, we found that increased blood pressure contributes to cardiac morphological and functional abnormalities, and that patients in the high-normal group had significant concentric morphologic changes in the left ventricle, as well as a tendency toward impairment of diastolic function. Thus, slight increases of blood pressure, even before hypertension occurs, can cause adaptive changes of the left ventricle. Therefore, the present findings support the JNC and WHO/ISH recommendations.

In the JNC-VI classification, a subset of optimal blood pressure among normotensives (120/80 mmHg or less) is included in addition to the subset of normal-range blood pressure (129/84 to 120/80 mmHg) (5). This classification is based on the epidemiological finding that the lower the blood pressure, the smaller the chance of developing cardiovascular disease (18, 19). In our study, no differences in the morphology and function of the left ventricle or the carotid artery were observed between the optimal and normal subsets. This suggests that blood pressure changes within normal levels do not induce a significant load on the large arteries or the heart.

Since the 1986 measurement of the combined intima and media thickness of arterial walls by Pignoli et al. (20), the need for evaluation of the level of atherosclerosis in the carotid artery of patients with various diseases has been widely accepted, and many reports have been published discussing the relationship between intimal-media thickness and hypertension (3), hyperlipidemia (21), and diabetes mellitus (22). Functional arterial changes are also readily examined by ultrasonography. Reports have described distension disorders of the conduit arteries in patients with ischemic heart disease or hypertension (3,13, 17). However, it is not known exactly when vascular changes occur during the progression of hypertension. In treating hypertension for the prevention of atherosclerotic morbid events, it is important to recognize the presence or absence of carotid arterial impairments. The results of the present study suggest that carotid artery intima-media hypertrophy, as well as abnormal distensibility of the artery, both of which may be related to elevated blood pressure, occur in the relatively early stage of hypertension.

Despite the fact that an increase in the internal diameter of the common carotid artery is observed during progression of hypertension (23), few longitudinal studies have been reported. In our study, enlargement of the common carotid artery diameter was observed only in the SII-III groups. Although the age was highest in this group, age itself was not a significant determinant of CAD. Since enlargement of the conduit carotid artery diameter has been regarded as vascular remodeling (24), its prog-

### Table 3. Correlation Coefficients in Linear Regression Analysis between Clinical Variables and Cardiovascular Morphological and Functional Abnormalities

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>BMI</th>
<th>SBP</th>
<th>DBP</th>
<th>TC</th>
<th>HDL</th>
<th>TG</th>
<th>FBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVMI</td>
<td>0.26**</td>
<td>ns</td>
<td>0.54**</td>
<td>0.54**</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>RWTd</td>
<td>ns</td>
<td>ns</td>
<td>0.50**</td>
<td>0.39**</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>A/E</td>
<td>0.65**</td>
<td>ns</td>
<td>0.54**</td>
<td>0.44**</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>IMT</td>
<td>0.54**</td>
<td>0.26**</td>
<td>0.49**</td>
<td>0.44**</td>
<td>ns</td>
<td>ns</td>
<td>0.26**</td>
<td>ns</td>
</tr>
<tr>
<td>Distens</td>
<td>-0.34**</td>
<td>ns</td>
<td>-0.59**</td>
<td>-0.45**</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; TC, total cholesterol; HDL, high-density lipoprotein; TG, triglyceride; FBS, fasting blood glucose level; LVMI, left ventricular mass index; RWTd, relative wall thickness at diastole; IMT, intimal-media thickness of common carotid artery; Distens, distensibility of common carotid artery; ns, not significant; **, p<0.01.

### Table 4. Coefficients (β) of Significant Equation Variables in Clinical Variables for Cardiovascular Morphological and Functional Abnormalities

<table>
<thead>
<tr>
<th></th>
<th>Equation variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>A/E (β=0.55), IMT (β=0.43)</td>
</tr>
<tr>
<td>SBP</td>
<td>RWTd (β=0.54), A/E (β=0.40), IMT (β=0.39), Distens (β=-0.48)</td>
</tr>
<tr>
<td>DBP</td>
<td>LVMI (β=0.70)</td>
</tr>
<tr>
<td>TG</td>
<td>IMT (β=0.22)</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride.
nostic significance remains to be investigated.

In conclusion, cardiac, but not vascular morphological adaptation and functional impairment were present even in subjects with high-normal blood pressure level, but there were no significant differences between the normal and optimal subsets. The results of the present study emphasize the clinical importance of focusing on the high normal subset when developing strategies to prevent morbidity and mortality in hypertension.

References