Gender-related Differences in Target Organ Damage in Untreated Patients with Essential Hypertension

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Abstract

We examined the gender-related differences in target organ damage in 220 untreated patients with essential hypertension (106 men and 114 women). As the indices of target organ damage, we examined the left ventricular mass index and the intima-media thickness in the carotid and femoral arteries obtained from echocardiography. In a multiple regression model, there was a significant positive correlation between the intima-media thickness and age in both groups. In men, there was a significant positive correlation between the left ventricular mass index and age, as well as the diastolic blood pressure, and body mass index. In women, there was a significant positive correlation between the left ventricular mass index and age, as well as plasma renin activity and smoking. In conclusion, there are gender-related differences in the contributing factors, which relate to left ventricular hypertrophy in patients with essential hypertension.

Key words: intima-media thickness, left ventricular hypertrophy, plasma renin activity, smoking

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Introduction

Recently, the differential impact of gender on the occurrence, prognosis and the response to treatment in cardiovascular disease has been reported (1-3). Despite an overall reduction in the death rate due to cardiovascular disease in the United States over the last several decades, the rate of decline is less for women than men (1). Due to an aging population, the absolute number of deaths due to cardiovascular disease in women is actually increasing (1). In the CADILLAC trial, the higher mortality rate in women compared with men after interventional treatment for acute myocardial infarction was reported (2). In the BEST study for the patients with heart failure, there was a trend for better survival in men than women in the ischemic patients (3).

As in men, the strong association between hypertension and cardiovascular disease in women has been demonstrated by a number of prospective studies (4, 5). In the general population, the target organ damage, such as left ventricular hypertrophy (LVH), the intima-media thickness (IMT) of the carotid artery and proteinuria are directly associated with an increased risk of cardiovascular disease (6-9). To our knowl-

edge, there are few reports about the gender-related differences in the prevalence of target organ damage and the contributing factors to target organ damage in the patients with essential hypertension.

We speculated the possibility of gender-specific therapies in the female patients with essential hypertension. In this study, we examined the gender-related differences in target organ damage and the related factors in untreated patients with essential hypertension.

Methods

The subjects were 220 patients with essential hypertension who were consecutively referred to the Division of Cardiology, the Department of Internal Medicine, Nishio Municipal Hospital between April 1997 and October 2004 (106 men and 114 women, mean age 55±10 years). All of the patients were previously untreated. The blood pressure was measured with an arm-cuff and a mercury sphygmomanometer after the patient had been resting in the sitting position for 5 minutes. Systolic and diastolic blood pressure measurements were taken as the first and fifth phase of the Korotkoff sounds, respectively. Hypertension was defined as

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Table 1. Clinical Characteristics in the 220 Hypertensive Patients and Comparison between Men and Women

	All (n=220)	Men (n=106)	Women (n=114)
Age	55 ± 10	54 ± 11	56 ± 9
Sex (men/women)	106/114		
Menopause in women	75 (66%)		
SBP (mmHg)	163 ± 20	161 ± 20	165 ± 19
DBP (mmHg)	97 ± 12	98 ± 12	96 ± 11
Pulse rate(/min)	70 ± 12	68 ± 13	71 ± 10
BMI (Kg/m ²)	24.6 ± 3.4	25.0 ± 3.3	24.3 ± 3.5
Duration of hypertension (year)	3.7 ± 6.6	3.8 ± 7.6	3.6 ± 5.6
Smoking	62 (28%)	49 (46%)	13 (11%)****
Plasma renin activity	0.97 ± 0.78	1.19 ± 0.94	0.76 ± 0.54****
Plasma aldosterone (pg/ml)	85.7 ± 38.8	92 ± 38	80 ± 39*
Fasting glucose (mg/dl)	107 ± 31	111 ± 40	104 ± 21
Hemoglobin A1c (%)	5.3 ± 0.8	5.3 ± 0.9	5.2 ± 0.7
Total cholesterol (mg/dl)	210 ± 34	204 ± 32	216 ± 35*
Triglyceride (mg/dl)	130 ± 78	152 ± 95	110 ± 49****
HDL-cholesterol (mg/dl)	58 ± 17	55 ± 19	62 ± 15**
Uric acid (mg/dl)	5.3 ± 1.4	6.0 ± 1.2	4.5 ± 1.1**

BMI: body mass index, DBP: diastolic blood pressure, SBP: systolic blood pressure. *p<0.05, **p<0.01, ****p<0.0001 vs. men.

Table 2. Target Organ Damage in the 220 Hypertensive Patients and Comparison between Men and Women

	ALL (n=220)	Men (n=106)	Women (n=114)
Echocardiographic findings:			
LVMI(g/m ²)	122 ± 42	136 ± 46	110 ± 34****
LVH (%)	139 (64%)	74 (70%)	65 (57%)*
RWT	0.44 ± 0.08	0.44 ± 0.08	0.43 ± 0.09
Retinal vascular change: (Keith-Wagener-Barker)			
grade 0	47 (21)%	21 (20%)	26 (23%)
grade 1	105 (48%)	49 (46%)	56 (49%)
grade 2	61 (28%)	34 (32%)	27 (24%)
grade 3	7 (3%)	2 (2%)	5 (4%)
Proteinuria	27 (12%)	16 (15%)	11 (10%)
Vascular echographic findings:			
Carotid artery			
max IMT (mm)	1.09 ± 0.65	1.14 ± 0.75	1.04 ± 0.54
Femoral artery			
max IMT (mm)	1.3 ± 0.8	1.44 ± 0.83	1.18 ± 0.76*

IMT: intima-media thickness, LVH: left ventricular hypertrophy, LVMI: left ventricular mass index, RWT: relative wall thickness.

*p<0.05, ****p<0.0001 vs. men.

a systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on two measurements taken with a 1-week interval. Patients who had evidence of secondary hypertension, valvular, coronary or primary myocardial disease, or a serum creatinine concentration >2 mg/dl were excluded.

Normotension was defined as systolic blood pressure < 130 mmHg and diastolic blood pressure < 85 mmHg. Twenty-four age- and sex-matched normotensive subjects (12 men and 12 women, mean age 54 ± 10 years) who had no history of hypertension and no evidence of cardiac disease served as controls.

As indices of target organ damage in the hypertensive patients, we examined left ventricular hypertrophy, atherosclerotic changes in the carotid and femoral arteries, retinal damage and proteinuria.

The hypertensive patients and normal subjects underwent echocardiographic measurement. Echocardiographic studies were carried out using a SONOS 4500 echocardiograph with a 3.5-MHz transducer (Philips Medical Systems, Bothell, WA) in the left lateral decubitus position. Left ventricular dimensions were taken from at least three cycles according to the Penn convention measurements (10, 11). These included the left ventricular end-diastolic diameter (LVEDD), the interventricular septal thickness (IVST) and the posterior wall thickness (PWT). The left ventricular mass was derived from the Penn conventions and the following formula: left ventricular mass (g) = $1.04 [(LVEDD + IVST + PWT)^3 - LVEDD^3] \div 13.6$ (10, 11). The left ventricular mass index (LVMI) was calculated by dividing the left ventricular mass by the body surface area. For the measurement of relative wall thickness,

LVEDD, IVST and PWT were measured according to the American Society of Echocardiography guidelines (12). Relative wall thickness was calculated as follows: relative wall thickness (RWT) = $(IVST + PWT) / LVEDD$.

In hypertensive patients, we examined the ultrasonographic scanning of the carotid and femoral arteries to record the most advanced atherosclerotic lesion according to the methods of Wendelhag et al (13, 14). The bilateral carotid and femoral arteries were investigated in the longitudinal and the transverse projections using a SONOS 4500 echocardiograph with a 7.5-MHz transducer. The IMT was defined as the distance from the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface of the far wall. The measurement of IMT in the common carotid artery was made along a 10-mm-long section just proximal to the carotid bulb. In the common femoral artery, measurements were made along a 15-mm-long section proximal to the bifurcation. At each longitudinal projection, IMT was measured from the site of the greatest thickness. The three determinations were averaged.

An ophthalmologist who was blinded to the blood pressure levels and echocardiographic data carried out the ophthalmoscopic examination. The retinopathic changes were assigned to four categories according to the Keith-Wagener-Barker scale (15).

Midstream urine samples collected in the morning after an overnight fast were immediately examined for protein in a semiquantitative fashion, and scored as -, $\pm$, +, ++ or +++, using a chemical reagent strip, the "Multistix 9 SG" (Bayer-Sankyo Co., Tokyo, Japan).

In the hypertensive patients, we examined the clinical characteristics that are thought to be related to target organ

Table 3. Univariate Correlation of the LVMI and Clinical Variables in the Hypertensive Patients

	All (n=220)	Men (n=106)	Women (n=114)
Age	0.183**	0.251**	0.192*
Male gender	0.310****		
SBP	0.223***	0.363****	0.148
DBP	0.226***	0.311**	0.082
BMI	0.226***	0.258**	0.146
Plasma renin activity	0.225***	0.112	0.242**
Plasma aldosterone	0.083	0.009	0.070
Total cholesterol	-0.152*	0.136	0.076
Triglyceride	0.068	0.028	0.012
HDL-cholesterol	0.145*	0.092	0.093
Uric acid	0.204**	0.043	0.045
Smoking	0.291****	0.183	0.311***

*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

Other abbreviations as in Tables 1 and 2.

Table 5. Stepwise Multiple Regression Analysis of Independent Variables that May Influence the LVMI and the IMT of the Femoral Artery in the 220 Hypertensive Patients

	F	Partial correlation coefficient
LVMI		
Age	36.401	0.364
Male gender	6.202	0.158
DBP	17.405	0.248
BMI	11.329	0.196
Plasma renin activity	7.149	0.163
Total cholesterol	4.936	-0.128
Smoking	11.645	0.209
Max IMT of femoral artery		
Age	36.616	0.377
Male gender	10.564	0.202
Multivariate prediction:		
LVMI = -92.769 + 1.477 (age) + 13.203 (male gender) + 0.89 (DBP) + 2.414 (BMI) + 8.706 (plasma renin activity) - 0.156 (total cholesterol) + 19.415 (smoking); adjusted R ² = 0.311, p<0.0001.		
Max IMT of femoral artery = -0.468 + 0.029 (age) + 0.323 (male gender); adjusted R ² = 0.160, p<0.0001.		
Abbreviations as in Tables 1 and 2.		

Table 4. Univariate Correlation of the the MAX IMT of the Femoral Artery and Clinical Variables in the Hypertensive Patients

	All (n=220)	Men (n=106)	Women (n=114)
Age	0.356****	0.433****	0.316***
Male gender	0.164*		
SBP	0.074	0.122	0.060
DBP	0.103	0.109	0.126
BMI	0.006	0.087	0.060
Plasma renin activity	0.040	0.119	0.047
Plasma aldosterone	0.089	0.132	0.103
Total cholesterol	0.070	0.058	0.030
Triglyceride	0.019	0.031	0.020
HDL-cholesterol	0.130	0.169	0.012
Uric acid	0.099	0.076	0.111
Smoking	0.124	0.018	0.145

*p<0.05, ***p<0.001, ****p<0.0001.

Other abbreviations as in Tables 1 and 2.

Table 6. Stepwise Multiple Regression Analysis of Independent Variables that may Influence the LVMI and the IMT of the Femoral Artery in the 106 Male Hypertensive Patients

	F	Partial correlation coefficient
LVMI		
Age	23.364	0.425
DBP	18.681	0.371
BMI	13.003	0.310
Max IMT of femoral artery		
Age	23.977	0.433
Multivariate prediction:		
LV mass index = -203.775 + 1.734 (age) + 1.399 (DBP) + 4.326 (BMI); adjusted R ² = 0.311, p<0.0001		
Max IMT of femoral artery = -0.295 + 0.032 (age); adjusted R ² = 0.180 p<0.0001.		
Abbreviations as in Tables 1 and 2.		

determined as weight (kg) divided by height (m) squared.

The venous blood samples were obtained after 30 minutes of rest in the supine position. Plasma renin activity and aldosterone concentration were measured by radioimmunoassay with a gamma counter. The blood glucose concentration was measured using the glucose oxidase immobilized membrane-hydrogen peroxide electrode peak acceleration method with an autoanalyzer (ADAMS-Glucose GA-1170 ARKRAY Co., Kyoto, Japan). Hemoglobin A1c was analyzed on the ADAMS-A1c HA-8160(ARKRAY Co.) based on the HPLC method. The serum total cholesterol and uric acid concentrations were measured by novel enzymatic

damage, i.e., age, sex, systolic blood pressure, diastolic blood pressure, body mass index, duration of hypertension, smoking, plasma renin activity, plasma aldosterone concentration, fasting blood glucose concentration, hemoglobin A1c, serum total cholesterol concentration, serum triglyceride concentration, serum high-density lipoprotein (HDL)-cholesterol concentration and serum uric acid concentration. The body mass index was selected as a measure of obesity,

Table 7. Stepwise Multiple Regression Analysis of Independent Variables that may Influence the LVMI and the IMT of the Femoral Artery in the 114 Female Hypertensive Patients

	F	Partial correlation coefficient
LVMI		
Age	10.485	0.284
Plasma renin activity	9.091	0.268
Smoking	11.226	0.288
Max IMT of femoral artery		
Age	12.459	0.316

Multivariate prediction:
 LV mass index = $36.060 + 1.020 (\text{age}) + 16.789 (\text{plasma renin activity}) + 30.346 (\text{smoking})$;
 adjusted $R^2 = 0.188$, $p < 0.0001$.
 Max IMT of femoral artery = $-0.260 + 0.025 (\text{age})$; adjusted $R^2 = 0.092$, $p < 0.001$
 Abbreviations as in Tables 1 and 2.

methods with an auto-analyzer (HITACHI-7180, Hitachi Medical Co., Tokyo, Japan). Using the same autoanalyzer, the serum triglyceride concentrations were measured using the free glycerol elimination enzymatic method, and the serum HDL-cholesterol concentration was measured using a chemical modification enzymatic method.

The data are expressed as mean values ± 1 SD. The statistical evaluation was performed with the unpaired t-test or chi-square test. Univariate correlations were analyzed using Pearson's correlation coefficient. We performed a forward stepwise regression analysis to select appropriate independent variables producing the highest partial correlation with the indices of target organ damage in the hypertensive patients. A p value of less than 0.05 was taken to indicate a significant difference.

Results

In 24 age- and sex-matched normotensive subjects, the LVMI in the men was 81 ± 16 g/m², and the LVMI in the women was 78 ± 10 g/m². RWT was 0.33 ± 0.04 . The upper normal limits for the LVMI (estimated as 2 SD above the mean values of the 24 normal subjects) were 113 g/m² in men and 98 g/m² in women. LVH was considered present if the LVMI exceeded 113 g/m² in men or 98 g/m² in women.

Table 1 shows the clinical characteristics in the 220 hypertensive patients. In the 114 hypertensive women, 75 women (66%) were post-menopause. Table 2 shows the indices of target organ damage in the 220 hypertensive patients. Sixty-four percent of all the patients had LVH according to echocardiography.

Table 1 shows a comparison of the clinical characteristics between men and women. Age, systolic blood pressure, diastolic blood pressure, pulse rate, body mass index, duration of hypertension, fasting glucose concentration and hemoglo-

bin A1c were equal between the men and women. Smoking was more prevalent in men than in women. Plasma renin activity, plasma aldosterone concentration, plasma triglyceride concentration and plasma uric acid were significantly higher in men than in women. Contrary to these findings, the plasma total cholesterol concentration and plasma HDL-cholesterol concentration were significantly higher in women than in men.

Table 2 shows a comparison of the indices of target organ damage between men and woman. LVMI was significantly higher in men than in women. LVH was more prevalent in men than in women. RWT, the retinal vascular change and the incidence of proteinuria were equal between the two groups. Although the max IMT of the carotid artery was equal between the two groups, the max IMT of the femoral artery was significantly thicker in men than in women.

Table 3 shows the results of the univariate correlation of the LVMI and clinical variables in the hypertensive patients. In all hypertensive patients, age, male gender, systolic blood pressure, diastolic blood pressure, body mass index, plasma renin activity, HDL-cholesterol, uric acid and smoking correlated significantly with the LVMI. In men, age, systolic blood pressure, diastolic blood pressure and body mass index correlated significantly with the LVMI. In women, age, plasma renin activity and smoking correlated significantly with the LVMI.

Table 4 shows the results of the univariate correlation of the max IMT of the femoral artery and clinical variables in the hypertensive patients. In all hypertensive patients, age and male gender correlated significantly with the max IMT. In both men and women, only age correlated significantly with the max IMT.

Table 5 shows the results of the multivariate analysis of independent variables that may influence the LVMI and the max IMT of the femoral artery in the 220 hypertensive patients. Age, male gender, diastolic blood pressure, body mass index, plasma renin activity and smoking were positively related to the LVMI. In the max IMT of the femoral artery, age and male gender were significantly associated.

Table 6 shows the results of the multivariate analysis of independent variables that may influence the LVMI and the max IMT of the femoral artery in the 106 male hypertensive patients. Age, diastolic blood pressure and body mass index were positively related to LVMI. Only age was positively related to the max IMT of the femoral artery.

Table 7 shows the results of the multivariate analysis of independent variables that may influence the LVMI and the max IMT of the femoral artery in the 114 female hypertensive patients. Age, plasma renin activity and smoking positively related to LVMI. In the max IMT of the femoral artery, only age was significantly associated.

Discussion

In our study, we found that LVH and the max IMT of the femoral artery are more prominent in men than in women in

the hypertensive patients. Next, we found that there were differences of the factors related to LVH between men and women in the hypertensive patients. In LVMI, age, plasma renin activity and smoking were positively related in women. Contrary to these findings, age, diastolic blood pressure and body mass index related positively to LVMI in men. Third, in the IMT of femoral arteries, only age related positively in both men and women.

Recently, there have been several reports concerning the gender-related differences in the influence of left ventricular hypertrophy on survival (16, 17). It was reported that LVH has a greater impact on survival in women than in men both in the patients with and without coronary artery disease (16, 17). Liao et al reported a gender-related difference in the contribution of LVH to mortality in the 436 consecutive patients free of angiographic coronary artery disease (17). For cardiac death, the relative risk of LVH was 1.3 and 7.5 in men and women, respectively. There was a significant gender-related difference in the contribution of LVH to survival. We thought that it was important to evaluate the gender-related differences of contributing factors to LVH in the hypertensive patients.

There have been several reports about the factors related to LVH, such as blood pressure (clinic blood pressure, 24-hour ambulatory blood pressure, blood pressure during stressful conditions), sympathetic nervous activity, plasma renin activity, plasma aldosterone concentration, body mass index and aging (18-24). The two major factors in the pathogenesis of LVH postulated on the basis of experimental results are hemodynamic and non-hemodynamic factors (24). Blood pressure is thought to be a hemodynamic factor. Plasma renin activity is thought to be non-hemodynamic. In our study, not a hemodynamic factor, but a non-hemodynamic factor, was related to LVH in the hypertensive women.

It is well known that the plasma renin profile holds much important information for therapy and prognosis in hypertensive patients (25-29). It was reported that a high plasma renin activity in hypertensive patients is associated with the risk of myocardial infarction (25, 26). Alderman et al reported a prospective trial involving 1717 patients with mild-to-moderate hypertension followed-up for 8.3 years (25). The heart attack rate of the high-renin patients was 3.2 times higher than that of the low-renin patients (25). There is much experimental and clinical evidence relating plasma renin-angiotensin levels to cardiovascular damage (26).

Conversely, several reports have suggested that salt sensitivity increases the risk of cardiovascular disease and all causes of mortality (27-29). It was reported that low-renin hypertension is associated with salt sensitivity (30, 31). Morimoto et al assessed the salt sensitivity in about 350 Japanese patients with essential hypertension (28). They reported that LVH was found more frequently in the salt-sensitive group than in the non-salt-sensitive group, and cardiovascular events occurred more frequently in patients with salt-sensitive hypertension (28). These results seem to con-

flict with the results of the study by Alderman et al (25, 28).

In the present study, the plasma renin activity was significantly higher in men than in women, and the plasma renin activity was related to LVH only in the hypertensive women. Our study results showing that target organ damage was more severe in men than in women may be explained partially by the high plasma renin activity in men. Because we did not examine the protocol for the diagnosis of salt sensitivity, we cannot evaluate the influence of salt-sensitive hypertensive patients on our study results. Although we cannot explain the exact reason for the positive relationship between plasma renin activity and LVH in the hypertensive women, there is the possibility that the plasma renin profile has key information to appropriate gender-specific hypertensive therapy and prognosis.

There have been several reports concerning the gender-specific treatment of hypertension (32-34). Gueyffier et al reported the meta analysis of hypertensive individual patient data according to sex, treatment with beta-blockers and thiazide diuretics (33). In their study, the absolute risk reduction due to treatment was not the same for women and men (33). For women, the absolute risk reduction was seen primarily for strokes, whereas in men, treatment prevented both strokes and coronary events (33). They concluded that the absolute benefit treatment for strokes and coronary events cannot be predicted across the sexes, and physicians need appropriate tools for predicting untreated risk in order to individualize hypertensive and other preventive therapies (33). Recently, Wassertheil-Smoller et al reported the association between cardiovascular outcomes and antihypertensive drug treatment in 30,219 older women (34). Among women with hypertension, but no history of cardiovascular disease, a 2-drug-class regimen of calcium channel blockers plus diuretics was associated with a higher risk of cardiovascular disease mortality vs. beta-blockers plus diuretics (34). Risks were similar for ACE inhibitors plus diuretics and beta-blockers plus diuretics (34). Although the role of the plasma renin activity in the prognosis was not evaluated in these studies, they suggested the possibility of gender-specific drug therapies in hypertensive patients (33, 34). Further studies for gender-specific treatment in hypertensive patients are needed.

Prescott et al reported that female smokers have a higher relative risk of myocardial infarction than male smokers, even after adjustment for major cardiovascular risk factors (35). Our study result of the relationship between LVH and smoking in hypertensive women may be related to the gender-related differences of the prognostic significances of smoking.

Stensland-Bugge et al examined the age and gender-related differences in the relationship between inherited and lifestyle risk factors and subclinical carotid atherosclerosis in the general population (36). The carotid IMT is thicker in men than in women across all ages (36). Age, systolic blood pressure, total cholesterol, HDL cholesterol, body mass index and smoking were independent predictors of IMT in

both sexes (36). These findings are compatible with our findings.

There are several limitations in our study. This was a retrospective study. Although the age between men and women was matched in our study, two-thirds of hypertensive women had undergone menopause. We were unable to examine the effect of menstruation in our study. We could not speculate about the reason why not carotid IMT, but only femoral IMT, was significantly different between both sexes. Although the condition of blood collection was equal between men and women, the plasma renin activity had been found to be affected by several factors, such as the sodium

intake (22). We did not examine the indices of sodium intake. Recently, there have been several reports concerning the relationship between aldosterone and cardiac structure (19, 20). In our study, there was no significant relationship between LVH and the plasma aldosterone concentration either in men or women. The reason for this is not clear.

In conclusion, there are gender-related differences in the contributing factors, which relate to LVH in patients with essential hypertension. These differences, such as plasma renin activity, may have clinical implications for gender-specific treatment in hypertensive patients.

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