Original Article

Sex-Related Differences in the Relations of Insulin Resistance and Obesity to Left Ventricular Hypertrophy in Japanese Hypertensive Patients

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Echocardiographically determined left ventricular (LV) hypertrophy is a powerful, independent predictor of cardiovascular morbidity and mortality. Both insulin resistance and obesity have a well-known association with LV hypertrophy. However, whether or not there are sex-related differences in the relations of insulin resistance and obesity to LV hypertrophy has never been systematically explored in Japan. We enrolled 91 never-treated hypertensive patients (49 men and 42 women) to assess the possible relations of insulin resistance and obesity to LV geometry. Insulin resistance was estimated using the homeostasis model assessment (HOMA) formula. Echocardiographically determined LV mass and relative wall thickness were measured as markers of LV geometry. In addition, body mass index (BMI) was calculated as weight (kg) divided by height (m)^2 as a marker of obesity. Independent determinants of LV mass in male hypertensive patients were HOMA value ($p<0.0001$) and age ($p=0.034$). BMI did not bear a significant relation to LV mass. In comparison, in female hypertensive patients BMI was an independent determinant of LV mass ($p=0.011$). The HOMA value did not bear a significant relation to LV mass in the female hypertensive patients. In conclusion, these findings indicate the presence of sex-related differences in the relations of insulin resistance and obesity to LV hypertrophy in Japanese hypertensive patients. The effect of obesity on LV geometry was greater in female hypertensive patients than in male hypertensive patients. (*Hypertens Res* 2006; 29: 499–504)

***Key Words*: essential hypertension, insulin resistance, obesity, left ventricular mass, gender**

Introduction

Echocardiographically determined left ventricular (LV) hypertrophy is known to be a powerful, independent risk factor of future cardiovascular morbidity and mortality in essential hypertension (*1–3*). Furthermore, there is increasing evidence of a link between LV hypertrophy and hypertensive target organ damage (*4–6*). The mechanisms through which LV hypertrophy increases cardiovascular risk are only partially understood, but might involve increased insulin resistance, which is increasingly recognized as an important predictor of cardiovascular morbidity and mortality (*7*, *8*).

The Framingham Heart Study (*9*), a cross sectional study of 3,799 participants, found that LV mass and wall thickness increased with worsening glucose intolerance, an effect that was more striking in women compared with men. This relation was largely accounted for by obesity. The combination of

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Received January 13, 2006; Accepted in revised form March 31, 2006.

Table 1. Patients Characteristics

	Male hypertensive patients (n=49)	Female hypertensive patients (n=42)
Age (years)	59±12	63±9
Pulse rate (beats/min)	68±12	70±10
Blood pressure (mmHg)		
Systole	161±14	159±14
Diastole	90±12	87±10
Pulse pressure (mmHg)	71±13	72±15
Body mass index (kg/m^2)	24.5±2.9	23.9±3.6

Values are mean±SD.

Table 2. Sex-Related Differences in Biochemical Characteristics in Hypertensive Patients

	Male hypertensive patients (n=49)	Female hypertensive patients (n=42)
Fasting plasma glucose (mmol/l)	5.44±0.78	5.33±0.50
Fasting immunoreactive insulin (pmol/l)	53.81±24.40	41.61±15.79*
HOMA value	1.87±0.99	1.38±0.62*
Total cholesterol (mmol/l)	4.99±0.83	5.59±1.01*
HDL-cholesterol (mmol/l)	1.14±0.34	1.40±0.41*
Triglycerides (mmol/l)	1.58±0.63	1.38±0.45

Values are mean±SD. *$p<0.01$ *vs*. male hypertensive patients. HOMA, homeostasis model assessment; HDL, high-density lipoprotein.

obesity and hypertension is more consistently associated with LV hypertrophy than either stimulus alone (*10*). Furthermore, we have previously reported that there is a sex-related difference in the relation of serum uric acid level and LV mass in hypertensive patients (*11*). Although an association of increased LV mass with adverse outcomes has been consistently reported in men and women, whether or not the relative impacts of insulin resistance and obesity on the prevalence of LV hypertrophy are similar in the two sexes has never been systematically explored in Japan.

Accordingly, we examined the sex-related differences in the relations of insulin resistance and obesity to LV hypertrophy identified by echocardiographically determined LV mass in nondiabetic and never-treated patients with essential hypertension.

Methods

Study Population

The study population included 91 nondiabetic patients with essential hypertension (49 men and 42 women; mean age: 61±10 years old). They had normal findings on a chemical screening battery and were nondiabetic by the criteria of the American Diabetes Association (*12*). All study patients participated in this study after giving informed consent. The study was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association. To exclude the presence of secondary forms of hypertension, all patients underwent a complete medical history, physical examination, and appropriate laboratory evaluation (*4*).

Physical Examinations

Physical examinations in hypertensive patients were supervised by the nursing staff. Weight and height were measured while the subjects were fasting overnight and wearing only underwear. Body mass index (BMI) was calculated as weight (kg) divided by height (m)^2. Blood pressure (BP) was measured in triplicate by a single physician who was expert in the evaluation of hypertension, with an appropriate arm cuff and a mercury sphygmomanometer after 5 min of rest in the sitting position. The arithmetic mean of the last two measurements was calculated. Korotkoff phase V was taken for diastolic blood pressure. Hypertension was defined as systolic BP (SBP) equal to or greater than 140 mmHg and/or diastolic BP (DBP) equal to or greater than 90 mmHg (*13*).

Biochemical Measurements

In the morning, after an overnight fast, venous blood was sampled for the measurement of plasma concentrations of glucose and insulin, and serum concentrations of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG). Plasma glucose was immediately determined by the glucose oxidase method. Plasma insulin was determined in duplicate by a highly specific and sensitive immunoradiometric assay (Abbott Japan; intraassay coefficient of variation (CV): 1.6%; interassay CV: 2.2%). Serum concentrations of TC, HDL-C and TG were assessed by standard enzymatic methods.

Insulin resistance was assessed from fasting immuno-reactive insulin (FIRI) and fasting plasma glucose (FPG) using the previously validated homeostasis model assessment (HOMA) (*14*) according to the following formula: HOMA value = FIRI (pmol/l) × FPG (mmol/l)/161.

Echocardiographic Measurements

Two-dimensionally guided M-mode echocardiography was performed by standard methods as previously outlined (*4*) using an SSD-6500 echocardiograph with a 3.5 MHz transducer (Aloka Inc., Tokyo, Japan). Echocardiographic examinations were performed and interpreted by the same

Table 3. Sex-Related Differences in Echocardiographic Characteristics in Hypertensive Patients

	Male hypertensive patients (n=49)	Female hypertensive patients (n=42)
LVM (g)	203±47	154±35$^{\#}$
LVM index (g/m^2)	120±26	102±21**
Relative wall thickness	0.41±0.10	0.37±0.07*
Percent FS (%)	36.5±7.0	38.1±6.5
SV/PP ratio	1.11±0.33	1.05±0.29

Values are mean±SD. *p<0.01, **p<0.001, and $^{\#}p$<0.0001 *vs*. male hypertensive patients. LVM, left ventricular mass; FS, fractional shortening; SV, stroke volume; PP, pulse pressure.

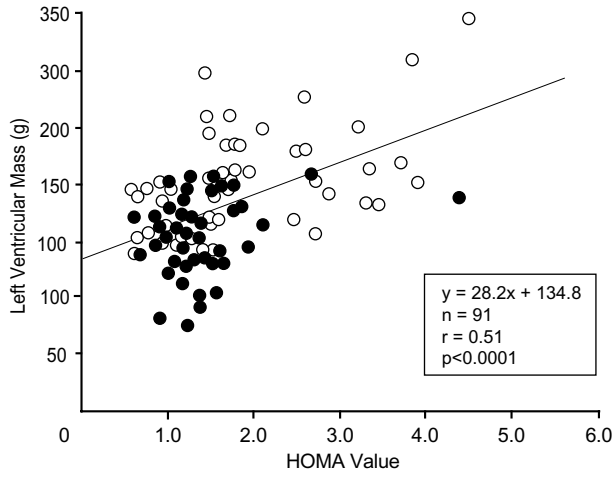

Fig. 1. *Relationship between the HOMA value and echocardiographically determined left ventricular mass in male hypertensive patients (open circles) and female hypertensive patients (closed circles). A statistically significant positive relation was found between the HOMA value and left ventricular mass in all hypertensive patients.*

cardiologist, who was unaware of the patient's data. LV internal dimension (LVID) and interventricular septal thickness (IVST) and posterior wall thickness (PWT) were measured at end-diastole and end-systole, according to the American Society of Echocardiography guidelines (*15*). LV mass was calculated according to a necropsy-validated formula (*16*). LV mass was also indexed by body surface area (BSA). Relative wall thickness (RWT) was measured as follows: RWT = 2 × (PWTd/LVIDd), where d is end-diastole. Percent fractional shortening (FS) was calculated as (LVIDd − LVIDs)/LVIDd × 100 and was used as an indicator of LV systolic function, where d and s are end-diastole and end-systole, respectively. End-diastolic and end-systolic LV volumes were calculated by the Teichholz method (*17*) using linear measurements at diastole and systole; this method has been validated by invasive and Doppler reference standards. Stroke volume (SV) was calculated as (end-diastolic LV volume − end-systolic LV volume). The ratio of SV to pulse pressure (PP) was used as an indirect measure of aortic compliance (*18*).

Statistical Analysis

All values are expressed as the mean±SD. Two-tailed unpaired Student's *t*-test was used to compare study response variables between categories. Correlation coefficients were calculated according to Pearson's method. A multiple regression analysis was also performed to select appropriate independent variables producing the highest partial correlation with LV mass in hypertensive patients. Probability values <0.05 were considered statistically significant in all analyses.

Results

Sex-Related Differences in Demographic and Clinical Characteristics

There were no significant differences in age, pulse rate, SBP, DBP, PP, and BMI between male and female hypertensive patients (Table 1).

Sex-Related Differences in Biochemical Characteristics

Although there was no significant difference in FPG between male and female hypertensive patients, FIRI and HOMA values in male hypertensive patients were significantly higher than those in female hypertensive patients. Both TC and HDL-C levels in female hypertensive patients were significantly higher than those in male hypertensive patients. There was no significant difference in TG level between the two hypertensive groups (Table 2).

Sex-Related Differences in Echocardiographic Characteristics

LV mass, LV mass index and RWT in male hypertensive patients were significantly larger than those in female hypertensive patients. There were no significant differences in percent FS and SV/PP ratio between male and female hypertensive patients (Table 3).

Subgroups Analysis

On the basis of the relationship between RWT and LV mass index, the 49 male and 42 female hypertensive patients were then divided into concentric, eccentric, and other hypertrophy groups. The partition values of 0.44 for RWT and 108 g/m^2 (male) or 104 g/m^2 (female) for LV mass index, which were

Table 4. Simple Correlation of Left Ventricular Mass with Demographic, Biochemical, and Ehchocardiographic Variables in Male and Female Hypertensive Patients

	Left ventricular mass			
	Male hypertensive patients (n=49)		Female hypertensive patients (n=42)	
	r values	p values	r values	p values
Age	0.224	0.1214	0.104	0.5122
Body mass index	0.138	0.3436	0.370	0.0157
Systolic blood pressure	0.218	0.1332	0.025	0.8755
Pulse pressure	0.056	0.7044	0.020	0.9017
Fasting plasma glucose	0.064	0.6636	0.083	0.6005
Immunoreactive insulin	0.563	<0.0001	0.319	0.0395
HOMA value	0.502	0.0002	0.278	0.0744
Precent fractional shortening	0.256	0.0755	0.177	0.2631
Stroke volume/pulse pressure ratio	0.070	0.6340	0.294	0.0586

HOMA, homeostasis model assessment.

Table 5. Multiple Regression Analysis of Factors Relevant to Left Ventricular Mass in Male and Female Hypertensive Patients

	Left ventricular mass					
	Male hypertensive patients (n=49)			Female hypertensive patients (n=42)		
	β	r values	p values	β	r values	p values
Age	0.265	2.193	0.034	0.149	1.020	0.314
Body mass index	0.058	0.482	0.632	0.392	2.680	0.011
Systolic blood pressure	0.193	1.607	0.115	0.018	0.125	0.901
HOMA value	0.526	4.336	<0.0001	0.269	1.852	0.072
	Multiple r^2=0.373, p=0.0003			Multiple r^2=0.236, p=0.037		

HOMA, homeostasis model assessment.

the mean + 2SD value of normotensive control subjects, were used (*4*). In male hypertensive patients, there were 17 (35%) patients with concentric hypertrophy and 15 (31%) with eccentric hypertrophy; in female hypertensive patients, there were 3 (7%) patients with concentric hypertrophy and 16 (38%) with eccentric hypertrophy. The prevalence of concentric hypertrophy in male hypertensive patients was significantly higher than that in female hypertensive patients.

Relations of Insulin Resistance, Demographic Factors and Percent FS to LV Mass

Figure 1 shows the relationship between the HOMA value and echocardiographically determined LV mass in hypertensive patients. As shown in Table 4, LV mass was significantly related to HOMA value and FIRI in male hypertensive patients. However, LV mass was related to BMI and FIRI in female hypertensive patients. In both sexes, LV mass was not related to age, SBP, PP, FPG, percent FS, or SV/PP ratio.

Table 5 shows the results of multiple regression analysis. Independent determinants of LV mass in male hypertensive patients were age and HOMA value. BMI did not bear a significant relation to LV mass. In contrast, in female hypertensive patients BMI was an independent determinant of LV mass. The HOMA value did not bear a significant relation to LV mass in the female hypertensive patients.

Discussion

In this cross-sectional study, LV mass correlated positively with the HOMA value in male hypertensive patients, but not in female hypertensive patients. In comparison, LV mass correlated positively with BMI in female hypertensive patients, but not in male hypertensive patients. These findings indicate the presence of sex-related differences in the relations of insulin resistance and obesity to LV hypertrophy in Japanese hypertensive patients.

It is widely acknowledged that peripheral hyperinsulinemia in patients with hypertension is a marker of insulin resistance (*19*, *20*). Bonora *et al*. (*21*) reported that diminished insulin sensitivity with regard to glucose utilization causes a substantial increase of insulin production in an attempt to maintain normal glucose utilization, making it possible that cardiovascular trophic effects and other actions of insulin could be exaggerated. They therefore calculated the HOMA value in order to obtain a better quantitative estimate of insulin resistance (*21*). In the present study, we showed an independent association between echocardiographically determined LV

mass and the HOMA value in male hypertensive patients, but not in female hypertensive patients. A potential limitation of the present study is that the insulin levels were assessed in the fasting state but not in response to glucose loading. Several studies have found a positive association between postload insulin levels or area under the postload insulin curve and LV structural variables (*22–24*).

In a recent investigation, the HOMA value was related to LV mass in women alone, but this relation was largely accounted for by obesity (*9*). In the present study, on the other hand, the HOMA value was related to LV mass in male hypertensive patients, but not in female hypertensive patients. Furthermore, this relation was not accounted for by BMI. If there is a sex-related difference in the impact of insulin resistance on LV mass, the underlying mechanism is unclear. One possibility is that insulin may have variable effects on LV geometry according to gender and race.

Verdecchia *et al*. (*24*) have reported that insulin and insulin growth factor-1 (IGF-1) were powerful independent determinants of LV mass in nondiabetic patients with hypertension. The direct effect of insulin on cardiac myocyte growth could be mediated at least in part, by IGF-1 receptors (*25*). Unfortunately, we were not able to measure IGF-1 binding protein in the present study. However, because the fasting insulin level was positively correlated to LV mass, our data suggest that insulin is a powerful determinant of cardiac myocyte growth in untreated patients with essential hypertension and normal glucose tolerance. In addition, hypertensive patients with glucose intolerance have more severe LV hypertrophy and LV diastolic dysfunction than those with normal glucose tolerance (*26*, *27*).

Obesity had a major impact on the development of LV hypertrophy in our female hypertensive patients. The increase in LV mass was statistically independent of age, blood pressure and insulin resistance. As expected from previous reports (*10*, *28*, *29*), the most prevalent LV geometric abnormality in obese patients with hypertension was eccentric LV hypertrophy. In the present study, although the most prevalent LV geometric abnormality in male hypertensive patients was concentric LV hypertrophy, the most prevalent LV geometric abnormality in female hypertensive patients was eccentric LV hypertrophy, confirming that the effect of obesity on cardiac anatomy is greater in women than in men (*30*).

Our multivariate analyses showed that the likelihood of LV hypertrophy identified by LV mass increases with age in male hypertensive patients. On the other hand, de Simone *et al*. have previously reported that increase in LV mass with age in women was associated with hemodynamic and hormonal changes that were not evident in men, suggesting a volume expansion occurring after menopause (*31*). Furthermore, the LV wall thickness and LV mass have been shown to significantly increase with advancing age in healthy normotensive subjects (*32*, *33*). Therefore, a possible explanation for the absence of an association between LV mass and age in our female hypertensive patients would be the small sample size. Another potential limitation of this study is its cross-sectional nature; in the future, it would be useful to perform a cardiovascular evaluation of individuals with previous serial data on LV geometry.

In conclusion, there is increasing evidence of a link between insulin and cardiovascular risk (*7*), although the independent role of insulin is still undetermined. The present study indicated the presence of sex-related differences in the relations of insulin resistance and obesity to LV hypertrophy in Japanese hypertensive patients. The effect of obesity on LV geometry was greater in female hypertensive patients than in male hypertensive patients.

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