

Effect of Insulin Resistance on Left Ventricular Structural Changes in Hypertensive Patients

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SUMMARY

Both left ventricular (LV) hypertrophy and insulin resistance (IR) have often been demonstrated in patients with essential hypertension (EH). Insulin may exert a direct growth promoting effect on cardiomyocytes rather than affecting the LV internal diameter. The purpose of this study was to examine the effect of IR on LV geometry.

We enrolled 105 patients (71 females, mean age, 49.2 ± 13.6 years) with recently diagnosed and untreated hypertension (blood pressure > 140 and/or 90 mmHg, fasting glucose < 110 mg/dL), and grouped them as normal (N) (39 patients, 26 females, mean age, 48.5 ± 14.7 years) if all M-mode echocardiographic measurements were within normal limits, concentric remodeling (CR) (22 patients, 15 females, mean age, 50.5 ± 14.8 years) if relative wall thickness was increased but left ventricular mass index (LVMI) was normal, concentric hypertrophy (CH) (13 patients, 9 females, mean age, 50.3 ± 10.8 years) if both ventricular thicknesses and the LVMI were increased, and eccentric hypertrophy (EH) (31 patients, 21 females, mean age, 48.6 ± 12.9 years) if ventricular thicknesses were normal, but LVMI was increased. Transthoracic echocardiography was performed in all subjects, and interventricular septal thickness (IVS), posterior wall thickness (PWT), sum of wall thickness (SWT), left ventricular end-diastolic internal diameter (LVED), relative wall thickness (RWT), and LVMI were recorded. Blood samples for routine biochemical examination and fasting insulin levels were obtained and then the homeostasis model assessment (HOMA) index was calculated by the formula: $\text{HOMA Index} = \text{Fasting Blood Glucose (mg/dL)} \times \text{Immunoreactive Insulin } (\mu\text{U/mL})/405$, for the assessment of IR.

There were no significant differences among the groups with respect to age, blood pressure (BP) levels, fasting blood glucose (FBG), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), total cholesterol (TC), or triglyceride (TG) levels. Insulin levels were significantly higher in the CR and CH groups in comparison with the N group ($P = 0.004$), and the HOMA index was higher in the CH group compared to the N group ($P = 0.024$). In Pearson's correlation analysis, insulin was found to be directly correlated with IVS ($r = 0.29$, $P = 0.002$), SWT ($r = 0.25$, $P = 0.009$), and RWT ($r = 0.33$, $P = 0.0001$). The HOMA index was also directly correlated with IVS ($r = 0.33$, $P = 0.001$), SWT ($r = 0.29$, $P = 0.002$), and RWT ($r = 0.29$, $P = 0.003$).

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Cardiac changes in hypertensive patients include increased LVMI and altered LV geometry. The concentric LV geometry seen in hypertensive patients might be mediated, at least in part, by increased insulin levels and the HOMA index. (Int Heart J 2006; 47: 391-400)

Key words: Hypertension, Left ventricular structure, Insulin resistance

LEFT ventricular (LV) hypertrophy¹⁻³⁾ and hyperinsulinemia/insulin resistance⁴⁾ are well known independent cardiovascular risk factors. Experimental evidence has also demonstrated that LV hypertrophy and insulin resistance are associated with pathophysiologic findings.⁵⁻⁷⁾ A wide spectrum of LV geometry has been reported in general population samples and in patients with essential hypertension.⁸⁻¹⁰⁾ Arterial hypertension represents, by itself, a fundamental stimulus for the development of left ventricular hypertrophy (LVH). However, LV overload imposed by arterial hypertension is more complex than expected, although in some patients LV mass increases, while in others it remains within normal limits. There is evidence that remodeling of the LV depends on the hemodynamic conditions of preload, afterload, LV contractility state, and severity and duration of the disease process.^{11,12)} Hypertrophy secondary to pressure overload has a great impact on the cardiovascular system and may develop with different patterns, generically called ventricular geometries. The latter depend on the relationship between wall thickness and ventricular cavity size. In the type known as “concentric remodeling,” wall thickness predominates over ventricular cavity size; in “eccentric hypertrophy,” the opposite relation takes place; and, finally, in “concentric hypertrophy,” both are increased. Ventricular mass is normal in the first type and increased in the other two. Arterial hypertension is known as a long lasting chronic overload that induces important structural changes in the ventricular myocardium.¹⁰⁾ On the other hand, some nonhemodynamic factors¹³⁾ such as genetic,^{14,15)} environmental,¹⁶⁾ and metabolic factors have also been suggested to affect LV mass and geometry. Among the metabolic factors, the presence of insulin resistance (IR)¹⁷⁻¹⁹⁾ has been found to be associated with LV growth. Most of the methods to measure IR are not feasible to use in large populations because they are expensive and time-consuming. Homeostasis model assessment (HOMA) is a new method that allows an easy and inexpensive assessment of IR.²⁰⁾

Accordingly, the present study was undertaken to assess the relationships between plasma insulin levels and various parameters of LV structure and function in recently diagnosed hypertensive, nondiabetic patients not taking any anti-hypertensive medication.

METHODS

One hundred and five consecutive patients (71 females, 34 males, mean age, 49.2 ± 13.6 years) with newly diagnosed essential arterial hypertension (mean arterial blood pressure; systolic, 150.9 ± 11.4 mmHg and diastolic, 99.4 ± 11.6 mmHg) were enrolled after informed written consent was obtained. Patients were considered to be hypertensive according to their clinical blood pressure levels (≥ 140 mmHg for systolic, and/or ≥ 90 mmHg for diastolic blood pressure as the mean of 3 different measurements in at least 3 different visits at 1-week intervals). Exclusion criteria from the study were a family history of diabetes and obesity (BMI must be < 30 kg/m²), coronary artery disease, congestive heart failure, valvular heart disease, impaired glucose tolerance, and diabetes mellitus. All patients were free from cardiac medications and drugs known to interfere with glucose metabolism and had a similar sedentary life style. The ethical committee of our institution approved the study.

Blood samples were taken after at least 10 hours of overnight fasting to determine fasting glucose and insulin levels. Fasting insulin concentrations were measured by radioimmunoassay. In the same session, serum samples were withdrawn to determine creatinine, fasting total cholesterol, high density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels. HOMA was calculated for the assessment of IR. The HOMA-index calculated by the formula according to the method developed by Matthews, *et al.*²⁰⁾ is as follows:

Fasting Blood Glucose (mg/dL) \times Fasting Immunoreactive Insulin (μ U/mL)/405.

Echocardiographic studies were performed on each subject using a commercially available Vivid 7 (General Electric) computed sonography system with 2.5 MHz transducer. The echocardiograms were obtained at rest with the subjects in the left lateral decubitus position. Two-dimensional guided M-mode measurements of left ventricular end-diastolic dimension (LVED), interventricular septum (IVS), and posterior wall thickness (PWT) were performed as recommended by the American Society of Echocardiography.²¹⁾ The sum of wall thickness was calculated as the sum of IVS and PWT, while relative wall thickness (RWT) was calculated as the ratio of the sum of wall thickness to left ventricular internal dimension. Left ventricular mass (LVM) was calculated according to the regression equation of Devereux, *et al.*: $0.80 \times (1.04 \times (\text{LVED} + \text{IVS} + \text{PW})^3 - (\text{LVED})^3) + 0.6$ gm.²²⁾ LV mass was indexed by body surface area; LVH was defined as an LV mass index (LVMI) of 125 g/m² in men²³⁾ and 110 g/m² in women.²²⁾ The patients were grouped as normal (N) (39 patients, 26 females) if all the wall thicknesses and LVMI were within the normal limits, as concentric remodeling (CR) (22 patients, 15 females) if RWT was increased ($\text{RWT} \geq 0.45$)²³⁾ and LVMI was

normal, as eccentric hypertrophy (EH) (31 patients, 21 females) if the opposite of CR was observed, and finally, as concentric hypertrophy (CH) (13 patients, 9 females), if both were increased. The same physician, who was unaware of other data relating to the subjects, made all the recordings.

Statistical analysis: All statistics were analysed using the SPSS 11.5 package programme. Differences among the groups were analysed by one-way analysis of variance followed by Tukey's test. The correlations among the HOMA index, insulin levels, and LV measurements were investigated by Pearson correlation analysis. A *P* value < 0.05 was regarded as being statistically significant.

RESULTS

We enrolled 105 patients (71 females, 34 males) with untreated recently diagnosed mild-to-moderate hypertension (150.9 ± 11.4 mmHg for systolic, 99.4 ± 11.6 mmHg for diastolic blood pressure). The patients were then classified as normal (39 patients, 26 females), concentric remodelling (22 patients, 15 females), concentric hypertrophy (13 patients, 9 females), and eccentric hypertrophy (31 patients, 21 females) according to the echocardiographic measurements. As shown in Table I, there were no differences concerning the clinical and metabolic variables among the groups except for the fasting insulin and HOMA index values, which were found to be significantly higher in the CR and CH groups for the first, and higher in the CH group for the latter in comparison with the normal group. Echocardiographic data for the groups are presented in Table II. As men-

Table I. Clinical and Metabolic Characteristics of Groups

	Normal	Concentric remodeling	Concentric hypertrophy	Eccentric hypertrophy	<i>P</i>
Number	39	22	13	31	
Age, years	48.5 ± 14.7	50.5 ± 14.8	50.3 ± 10.8	48.6 ± 12.9	NS
Gender (female/male)	26/13	15/7	9/4	21/10	NS
SBP, mmHg	150.7 ± 11.4	151.3 ± 11.9	151.5 ± 11.1	150.4 ± 12.1	NS
DBP, mmHg	99.7 ± 10.4	99.8 ± 11.3	98.9 ± 12.5	99.9 ± 11.4	NS
BMI, kg/m ²	26.7 ± 3.1	26.4 ± 4.1	26.1 ± 3.7	26.7 ± 3.2	NS
Fasting glucose (mg/dL)	95.5 ± 9.5	97.7 ± 9.3	101.3 ± 16.5	94.9 ± 9.5	NS
Fasting insulin, μU/mL	8.0 ± 1.9*	12.2 ± 7.4*	13.0 ± 2.8*	9.3 ± 2.8	0.004
HOMA-index	2.0 ± 0.8*	2.4 ± 1.0	3.1 ± 2.1*	2.2 ± 0.7	0.024
TC (mg/dL)	201.4 ± 33.6	201.5 ± 24.5	219.3 ± 32.2	208.8 ± 30.5	NS
TG (mg/dL)	146.6 ± 77.5	159.2 ± 68.2	157.1 ± 118.7	139.5 ± 40.1	NS
HDL-C (mg/dL)	55.8 ± 13.3	50.8 ± 10.0	51.5 ± 13.4	53.3 ± 10.5	NS
LDL-C (mg/dL)	114.7 ± 37.2	126.0 ± 37.6	133.5 ± 48.2	129.5 ± 30.3	NS

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; HOMA-index, homeostasis model assessment; TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein cholesterol; and LDL-C, low density lipoprotein cholesterol. Values are mean ± SD, *: difference between normal and other groups.

tioned above, all parameters were within normal limits in the N group, LVMI increased in the CH and EH groups, RWT, SWT, and IVS measurements increased in CR and CH, and LVED increased in the CH and EH groups, particularly the latter. Pearson's correlation analysis performed among the insulin levels and echocardiographic measurements showed positive and significant correlations between insulin levels and IVS ($P = 0.002$, $r = 0.29$), RWT ($P = 0.0001$, $r = 0.33$), and SWT ($P = 0.009$, $r = 0.25$), but no significant correlations with the other echocardiographic data (Table III). Again Pearson's correlation analysis was performed among the HOMA index and echocardiographic measurements, and revealed significant positive correlations with IVS ($P = 0.001$, $r = 0.33$), RWT ($P = 0.003$, $r = 0.29$), and SWT ($P = 0.002$, $r = 0.29$), but no significant correlations with the other echocardiographic data as shown in Table III. There were no significant correlations between the HOMA index, insulin levels, and body mass index ($P = 0.9, 0.8$), and systolic ($P = 0.07, 0.08$) or diastolic ($P = 0.08, 0.1$) blood pressures. The HOMA index values in the 4 different groups are shown in Figure 1. It can be seen that the HOMA index was significantly higher

Table II. Echocardiographic Parameters of Groups

	Normal	Concentric remodeling	Concentric hypertrophy	Eccentric hypertrophy	<i>P</i>
LVED (35-56 mm)	46.5 ± 3.3	42.5 ± 3.6	50.3 ± 3.0*	51.3 ± 4.4*	0.0001*
IVS (6.0-11 mm)	8.7 ± 1.1	10.7 ± 1.1*	12.5 ± 1.6*	9.8 ± 1.4	0.0001*
PWT (9.0-14 mm)	8.0 ± 1.0	10.6 ± 1.3	12.1 ± 1.3*	9.9 ± 1.1	0.0001*
LVMI (g/m ²)	89.5 ± 16.6	88.0 ± 14.6	141.6 ± 19.4*	128.6 ± 23.7*	0.0001*
RWT	0.37 ± 0.04	0.50 ± 0.04*	0.49 ± 0.04*	0.38 ± 0.05	0.0001*
SWT	17.5 ± 1.8	21.4 ± 1.4*	24.6 ± 2.0*	19.5 ± 2.0	0.0001*

LVED indicates left ventricular end-diastolic diameter; IVS, interventricular septal thickness; PWT, posterior wall thickness; LVMI, left ventricular mass index; RWT, relative wall thickness; and SWT, sum of wall thickness. *: significant difference with other groups.

Table III. Correlation Analysis Between Insulin, HOMA Index, and Echocardiographic Variables

		LVED	IVS	RWT	LVMI	PWT	SWT
Insulin	<i>r</i>	-0.14	0.29	0.33	0.016	0.13	0.25
	<i>P</i>	0.13	0.002	0.0001	0.87	0.17	0.009
HOMA index	<i>r</i>	-0.024	0.33	0.29	0.15	0.16	0.29
	<i>P</i>	0.8	0.001	0.003	0.11	0.08	0.002

LVED indicates left ventricular end-diastolic diameter; IVS, interventricular septal thickness; RWT, relative wall thickness; LVMI, left ventricular mass index; PWT, posterior wall thickness; and SWT, sum of wall thickness.

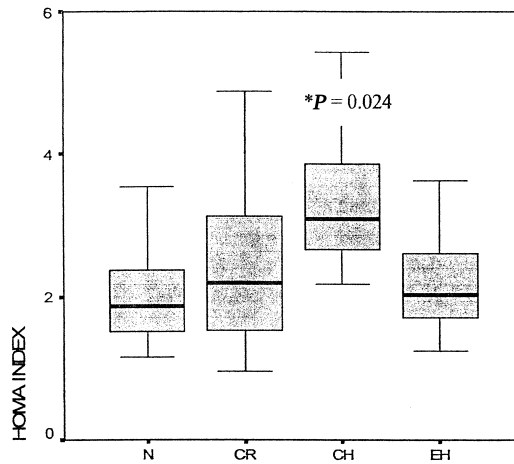


Figure 1. Homeostasis model assessment index (HOMA) measures of groups. N indicates normal; CR, Concentric remodelling; CH, Concentric hypertrophy; and EH, Eccentric hypertrophy.
* P = Significant in comparison with normal group.

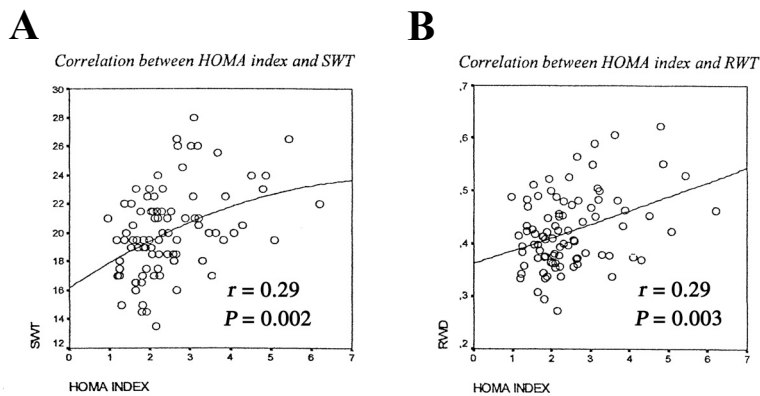


Figure 2. Correlation analysis between homeostasis model assessment index (HOMA) and sum of wall thickness (SWT) (A), and relative wall thickness (RWT) (B).

in the CH group compared to the normal group ($P = 0.024$). The correlations between the HOMA index and SWT ($P = 0.002$, $r = 0.29$) and RWT ($P = 0.003$, $r = 0.29$) are presented in Figure 2.

DISCUSSION

The correlations between measures of insulin resistance and left ventricular

structure have been studied in different populations with varying results. Significant relationships between insulin resistance and left ventricular mass have been reported in hypertensive populations.^{24,25)} However, other investigators have only found a weak correlation between these parameters²⁶⁾ or no association at all²⁷⁻²⁹⁾ after adjustments for covariates. Our study confirms that in hypertensive patients, there are correlations between LVMI, LV wall thicknesses, and IR, and they provide evidence that IVS, RWT, and SWT, but not the LVED, are the best echocardiographic parameters associated with fasting plasma insulin levels and the HOMA index, which is an insulin resistance parameter. Furthermore, a change in the echocardiographic patterns from normal to concentric hypertrophy, including concentric remodeling, is associated with a trend towards insulin resistance.

Previous studies have concluded that LV hypertrophy indicates a worse prognosis for hypertension.¹⁻³⁾ In fact, patients with increased LV mass have a greater risk of cardiovascular and all cause mortality than those with lower LV mass. Levy, *et al*¹⁾ also showed that this difference widened progressively over a 10-year follow-up, despite conventional antihypertensive therapy. Several but not all studies^{23,30-33)} have demonstrated a high risk of cardiovascular adverse events in patients with concentric LV hypertrophy and a low risk in those with normal LV geometry. Recent reports have demonstrated that the relationship between wall thickness and chamber diameter is of importance with respect to cardiovascular risk.^{22,34)} A concentric left ventricular pattern characterized by high relative wall thickness is associated with a poorer prognosis than eccentric hypertrophy in which the ratio between wall thickness and chamber diameter is normal. Epidemiological studies have shown that high fasting insulin levels are associated with an adverse cardiovascular outcome, independent of other risk factors,³⁴⁾ and this could be explained in part by a remodeling effect by insulin on left ventricular structure. It has been proposed that insulin may exercise its influence on cardiac geometry by acting as a growth factor³⁵⁾ and trophic effects by insulin on myocardial tissue have been demonstrated in cell cultures³⁶⁾ and animal models.³⁷⁾ Moreover, it has been suggested that hyperinsulinemia stimulates sympathetic nervous system (SNS) activity³⁸⁾ which may in turn affect ventricular structure directly, due to growth-stimulating effects, or indirectly, by contributing to increases in heart rate and blood pressure levels. Our study confirms the association of insulin action and degree of LV mass and also shows that patients with a normal LV pattern have a significantly better insulin action (lower fasting insulin levels and lower HOMA index) than patients with abnormal LV geometry. However, no significant differences among hypertensives with concentric remodeling and eccentric or concentric hypertrophy were found.

Furthermore, BMI, systolic and diastolic arterial blood pressures, and both LVM index and LVED had poor correlations with metabolic parameters, whereas

SWT and RWT were significantly correlated positively with the fasting insulin levels and HOMA index in correlation analysis. Such data support the hypothesis that the reason for the increase in wall thickness, which is a sign of myocardial structural change, and in part LV hypertrophy itself in hypertensive patients, might be due to the increased fasting insulin levels and HOMA index, which is an indicator of insulin resistance. Our data are in agreement with those of Barbagallo, *et al*³⁹⁾ showing an increase in ventricular wall thickness in insulin-resistant patients. Several pathophysiologic factors could be behind such an association. An insulin-mediated overdrive in sympathetic nervous system activity⁴⁰⁾ should be considered. The positive correlation between insulin levels and the HOMA index were substantially stronger with SWT and RWT than the LVM index. However, fasting insulin levels and the HOMA index were found to be significantly higher in concentric remodeling and concentric hypertrophy patients compared with the normal group. There were no differences between eccentric hypertrophy and the other groups for those parameters. Therefore, we can conclude that insulin acts through increases in wall thicknesses, rather than an increase in LVED during the LV geometric change process in hypertensive patients. Such an explanation may apply to these results. Another hypothesis is SNS overdrive, which is responsible for both insulin resistance and development of LVH.¹⁸⁾ In fact, hypertensive patients with LVH had higher plasma catecholamine concentrations than hypertensive patients without LVH and control subjects.⁷⁾ Whether SNS activity can affect our data remains unknown. On the other hand, our findings suggest that insulin resistance exerts its influence directly on myocardial walls, independently of LVED. Hyperinsulinemia might increase LV mass through its growth stimulating effect. In fact, insulin can bind and activate the insulin-like growth factor-1 receptor, thus resulting in increased DNA and protein synthesis as well as cell proliferation in many tissues.^{18,36)} In particular, it has been demonstrated that insulin stimulates the proliferation of vascular smooth cells and induces the hypertrophy of cardiomyocytes by increasing mRNA levels for muscle-specific genes (myosin light chain, O-actin, and troponin I) and stimulating protein synthesis.⁴⁰⁾ Therefore, it is plausible that hyperinsulinemia in hypertension could stimulate SNS activity, which may in turn affect ventricular structure directly, due to growth-stimulating effects, or indirectly, by contributing to increases in heart rate and blood pressure levels. However, further mechanistic studies are required in order to clarify the links between insulin resistance, compensatory hyperinsulinemia, and aberrations in cardiovascular structure.

In conclusion, cardiac changes in hypertensive people include increases in left ventricular mass, as well as altered left ventricular geometry. The concentric left ventricular geometry associated with hypertension appears to be mediated, at least in part, by increased insulin levels, and the HOMA index. The present

results might indicate that measurement of serum insulin levels and calculation of the HOMA index could provide insights into the pathogenesis of different LV geometries in patients with mild to moderate essential hypertension.

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