The Relation Between Insulin-Resistance and Left Ventricular Mass

THE RELATION BETWEEN INSULIN-RESISTANCE AND LEFT VENTRICULAR MASS IN HYPERTENSIVE PATIENTS

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ABSTRACT
Both left ventricular hypertrophy (LVH) 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 left ventricular internal diameter. The aim of this work was to examine the effect of IR on LV geometry in newly diagnosed arterial hypertension (NDAH), non diabetic patients not taking any antihypertensive medication. One hundred and eight subjects (66 males and 42 females) with mean age of 48.9±4.67 years were enrolled in the study; including 88 newly diagnosed hypertensive patients (54 males and 34 females) and 20 healthy control subjects. Hypertension was defined as elevation of blood pressure ≥ 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. Fasting glucose, insulin levels, total cholesterol, (HDL-C), and triglyceride (TG) levels. HOMA-index was calculated for the assessment of insulin resistance by the formula: Fasting Blood Glucose (mg/dL) × Fasting Insulin (µU/mL)/405. Two-dimensional guided M-mode echocardiography for measurements of left ventricular end-diastolic dimension (LVEDD), inter-ventricular septum thickness (IVST), posterior wall thickness (PWT), left atrial diameter (LAD), fraction of shortening (FS) and ejection fraction (EF). Left ventricular mass (LVM) and LV mass index (LVMI) was calculated .According to LVMI, hypertensive patients were classified into two groups; normal LV dimensions and LVH. So, we had three groups on our study: Hypertensive patients with normal LV dimensions included 46 patients (28 males and 18 females) with mean age 48.6±3.55 years, Hypertensive patients with LVH included 42 patients (26 males and 16 females) with mean age 49.8±3.72 years and Healthy control subjects included 20 subjects (12 males and 8 females) with mean age 47.7±7.74 years. Fasting blood insulin and HOMA-index were significantly higher in patients with LVH than patients with normal LV dimensions and than control subjects. PWT, IVST, LVM and LVMI were significantly higher in patients with LVH than in patients with normal LV dimensions and than control subjects. Other echocardiographic measures showed no significant difference between the study groups. We found highly significant positive correlations between insulin levels and IVS, PWT, LVM, and LVMI. Also, we found highly significant positive correlations between HOMA-index and IVS, PWT, LVM, and LVMI. There was no significant correlation between insulin level or HOMA-index and other echocardiographic parameters. We concluded that cardiac changes in hypertensive patients including increased wall thickness, LVM and LVMI. The concentric LV geometry seen in hypertensive patients might be mediated, at least in part, by increased insulin levels and the HOMA index.

Key words: Insulin resistance, HOMA index, Hypertension, Left ventricular hypertrophy.

INTRODUCTION
Left ventricular (LV) hypertrophy (1) and hyperinsulinemia/insulin resistance (2) are well known independent cardiovascular risk factors. A wide spectrum of LV geometry has been reported in general population samples and in patients with essential hypertension (2).

Newly diagnosed arterial hypertension contributes significantly to impairment of left ventricular diastolic function in obese patients before the development of structural aberrations detectable by echocardiography (3).

Hypertension represents, by itself, a fundamental stimulus for the development of left ventricular hypertrophy (LVH). However, with LV overload imposed by arterial hypertension, LV mass increases in some patients, while in others it remains within normal limits (4). On the other hand, some non hemodynamic factors such as genetic (5), environmental (6), and
metabolic factors have also been suggested to affect LV mass and geometry.

Among the metabolic factors, the presence of insulin resistance (IR) (7) has been found to be associated with LV growth. Homeostasis model assessment (HOMA) is a method that allows an easy and inexpensive assessment of IR (8).

AIM OF THE WORK was to examine the effect of IR on LV geometry in newly diagnosed arterial hypertension (NDAH), non diabetic patients not taking any antihypertensive medication.

METHODS

This study had been carried out in the Cardiology Department, Internal Medicine Department and the Echocardiography Unit of Zagazig University Hospitals.

One hundred and eight subjects (66 males and 42 females) with mean age of 48.9±4.67 years were enrolled in the study; including 88 newly diagnosed hypertensive patients (54 males and 34 females) and 20 healthy control subjects.

All the patients were newly diagnosed hypertensive patients. Hypertension was defined as elevation of blood pressure ≥ 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 (9).

Exclusion criteria from the study were a family history of diabetes, 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.

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 fasting total cholesterol, high density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels. HOMA was calculated for the assessment of insulin resistance. The HOMA-index calculated by the formula according to the method developed by Matthews, et al., (8) as following:

\[
\text{Fasting Blood Glucose (mg/dL)} \times \text{Fasting Insulin (µU/mL)}/405
\]

Echocardiographic studies were performed on each subject using a commercially Hewlett Pakard 5500 (HP. 5500) echo-set using a 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 (LVEDD), interventricular septum thickness (IVST), posterior wall thickness (PWT), left atrial diameter (LAD), fraction of shortening (FS) and ejection fraction (EF) were performed as recommended by the American Society of Echocardiography (8).

Left ventricular mass (LVM) was calculated according to the equation of Devereux, et al (10):

\[
0.80 \times [(1.04 \times (LVEDD + IVST + PWT)^3 - (LVEDD)^3] + 0.6 \text{ gm}
\]

LVM was indexed by body surface area; left ventricular hypertrophy (LVH) was defined as an LV mass index (LVMi) of 125 gm/m² in men and 110 gm/m² in women (11).

According to LVMi, hypertensive patients were classified into two groups; normal and LVH. So, we had three groups on our study:

**Hypertensive patients with normal LV dimensions:** this group included 46 patients (28 males and 18 females) with mean age 48.6±3.55 years.

**Hypertensive patients with LVH:** this group included 42 patients (26 males and 16 females) with mean age 49.8±3.72 years.

**Healthy control subjects:** This group included 20 subjects (12 males and 8 females) with mean age 47.7±7.74 years.
Statistical analysis: All statistics were analyzed using the SPSS 11.5 package program. Differences among the study groups were analyzed by student's t-test and χ²-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 108 subjects (66 females, 42 males) in the study, among them 20 healthy subjects and 88 patients with untreated recently diagnosed mild-to-moderate hypertension (151.5±5.37 mmHg for systolic, 97.8±3.78 mmHg for diastolic blood pressure).

As shown in Table I, there was no significant difference among the study groups concerning the clinical data, except for a highly significantly higher systolic and diastolic blood pressure in normal and LVH groups than control group.

Metabolic data are shown in table II. Fasting blood insulin and HOMA-index were significantly higher in patients with LVH than patients with normal LV dimensions and control subjects. Other metabolic data showed no significant difference among study groups.

Echocardiographic data are shown in table III. As shown; PWT, IVST, LVM and LVMI were significantly higher in patients with LVH than patients with normal LV dimensions and control subjects. Other measures showed no significant difference among study groups. Pearson’s correlation analysis performed among the insulin levels and echocardiographic measurements showed highly significant positive correlations between insulin levels and IVS (r = 0.35, p = 0.00083), PWT (r = 0.338, p = 0.00128), LVM (r = 0.367, p = 0.00044), and LVMI (r = 0.374, p = 0.00033), (Table IV).

Again Pearson’s correlation analysis was performed among the HOMA-index and echocardiographic measurements, and revealed highly significant positive correlations with IVS (r = 0.759, p <0.00001), PWT (r = 0.783, p <0.00001), LVM (r = 0.702, p <0.00001), and LVMI (r = 0.79, p <0.00001), (Table IV). Correlations between HOMA-index and LVM, LVMI are shown in figure Ia and Ib.

There was no significant correlation between insulin level or HOMA-index and other echocardiographic parameters.

<table>
<thead>
<tr>
<th>Table I: Clinical characteristics of study groups.</th>
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<tbody>
<tr>
<td>LVH (n = 42)</td>
</tr>
<tr>
<td>Age (ys)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
</tr>
<tr>
<td>Heart Rate (b/m)</td>
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<tr>
<td>Systolic Blood Pressure (mmHg)</td>
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<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
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</tbody>
</table>

Values are mean ± SD. * = p < 0.01 vs control.
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Figure 1-A

Figure 1-B

Table II: Metabolic characteristics of study groups

<table>
<thead>
<tr>
<th></th>
<th>Normal (n = 46)</th>
<th>LVH (n = 42)</th>
<th>Control (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>207.1±15.93</td>
<td>209.2±16.52</td>
<td>210±15.74</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>153.5±12.27</td>
<td>153.9±11.19</td>
<td>157.7±9.71</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>58.5±4.57</td>
<td>56.9±5.39</td>
<td>56.4±4.55</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>127.9±9.34</td>
<td>130.9±9.46</td>
<td>131.7±7.49</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dl)</td>
<td>93.1±10.11</td>
<td>94.8±10.49</td>
<td>96.7±10.24</td>
</tr>
<tr>
<td>Fasting blood insulin (mg/dl)</td>
<td>7.59±1.07</td>
<td>8.38±0.842 *</td>
<td>7.7±1.065</td>
</tr>
<tr>
<td>HOMA index</td>
<td>2.1±0.237 §</td>
<td>2.81±0.259 *</td>
<td>2.04±0.203</td>
</tr>
</tbody>
</table>

* = p < 0.01 vs control, § = p < 0.01 vs LVH.

HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; HOMA: homeostasis model assessment. Values are mean ± SD.
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DISCUSSION

LEFT ventricular hypertrophy (LVH) (1) and hyperinsulinemia /insulin resistance (IR) (2) are well known independent cardiovascular risk factors. Both LVH and IR have often been demonstrated in patients with essential hypertension (EH). A wide spectrum of LV geometry has been reported in general population samples and in patients with essential hypertension (2).

Our study confirmed 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. Our study also showed that in hypertensive patients, there were significant positive correlations between echocardiographic parameters of LVH such as IVST, PWT, LVM, LVMI and IR, measured with fasting plasma insulin levels and the HOMA index, which is an insulin resistance parameter.

There was no significant correlation between insulin level or HOME-INDEX and LVEDD.

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 (12).

However, other investigators have only found a weak correlation between these parameters (13) or no association at all (14) after adjustments for covariates.

Furthermore, a change in the echocardiographic patterns from normal to concentric hypertrophy, including concentric remodeling, is associated with a trend towards insulin resistance (4).

Previous studies have concluded that LV hypertrophy indicates a worse prognosis for hypertension. In fact, patients with increased LV mass have a greater risk of cardiovascular and all cause mortality than those with lower LV mass (1). Krumholz et al (15) 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 and this difference widened progressively over a 10-year follow-up, despite conventional antihypertensive therapy.

Epidemiological studies have shown that high fasting insulin levels are associated with an adverse cardiovascular outcome, independent of other risk factors (2) 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 factor and trophic effects by insulin on myocardial tissue have been demonstrated in cell cultures and animal models (16).

Moreover, it has been suggested that hyperinsulinemia stimulates sympathetic nervous system (SNS) activity (17) 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.

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. Several pathophysiologic factors could be behind such an association and an insulin-mediated overdrive in sympathetic nervous system activity should be considered (17).

Kaftan et al. (3) found that the positive correlation between insulin levels and the HOMA index were substantially stronger with sum of wall thickness (SWT) and relative wall thickness (RWT) than the LVM index and they concluded that insulin acts through increases in wall thickness, rather than an increase in LVED during the LV geometric change process in hypertensive patients although recent studies reported that an abnormalities of LV filling precede detectable structural changes and impairment of systolic function, they are considered one of the earliest signs of cardiac involvement in the presence of different cardiovascular risk factors (18). NDAH also plays an important role in LV diastolic dysfunction pathogenesis (19).

Another hypothesis is SNS overdrive, which is responsible for both insulin resistance and development of LVH (20). In fact, hypertensive patients with LVH had higher plasma catecholamine concentrations than hypertensive patients without LVH and control subjects (17).

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 (21). 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-
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specific genes (myosin light chain, O-actin, and troponin I) and stimulating protein synthesis (21).

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.

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.

REFERENCE


11- Koren MJ, Devereux RB, Casale PN, et al. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med 1991; 114: 345-352.


15- Krumholz HM, Larson M, Levy D. Prognosis of left ventricular geometric