Hyperinsulinaemia, regional adipose tissue distribution and left ventricular mass in normotensive, elderly, obese subjects


Cattedra di Geriatria, Istituto I Clinica Medica, Università ‘La Sapienza’, Rome, Italy

Obesity is a metabolic condition, related to abnormalities of the glyco-insulinaemic metabolism, and plays a substantial role in the development of cardiovascular disease. The aim of this study was to establish a correlation among left ventricular mass, evaluated echocardiographically according to Penn Convention criteria, blood pressure, evaluated by ambulatory blood pressure monitoring, anthropometric indices for evaluation of body mass index and waist to hip ratio circumference, regional adipose tissue distribution, evaluated by ultrasound measurements of visceral adipose tissue, and insulin resistance, evaluated by hyperinsulinaemia by oral glucose tolerance test.

We selected two groups of elderly male subjects well matched for age (68.5 ± 6.4 years): 29 obese and 20 lean, with a body mass index, respectively, of 34.6 ± 2.9 and 23.4 ± 2.3. Statistical analysis was carried out by Student’s t-test and linear regression analysis. In spite of the fact that statistical analysis showed a higher, though not statistically significant, systolic and diastolic mean blood pressure in the lean subjects, we found an increased left ventricular mass in obese subjects (P <0.0001). The area under the insulin curve was higher in obese than in lean subjects (P <0.0001) while the area under the glucose curve was not significantly different in the two groups. Furthermore, linear regression analysis showed that in obese subjects left ventricular mass was strictly correlated with visceral adipose tissue (r=0.670; P <0.0001) and hyperinsulinaemia (r=0.615; P <0.0001).

In conclusion, our data suggest that centripetal adipose tissue distribution and hyperinsulinaemia, independent of blood pressure values, are closely correlated with left ventricular mass. (Eur Heart J 1998; 19: 326–331)

Key Words: Left ventricular mass, obesity, hyperinsulinaemia, ambulatory blood pressure, ageing.

Introduction

Obesity in adults is associated with increased cardiovascular disease mortality[1,2], and is a condition, closely linked to hypertension[3], abnormalities of the glyco-insulinaemic metabolism, diabetes, decreased high-density lipoprotein levels and increased triglycerides[4,5]. Recently, increasing interest has been focused on the relationship between obesity and increased left ventricular mass, a powerful independent predictor of cardiovascular morbidity and mortality[6,7].

Several studies of obese adults have reported increased left ventricular mass, left ventricular wall thickness and left ventricular cavity size, compared with lean subjects[8]. Recent reports have shown an increased risk of the sequelae of cardiovascular disease in subjects with echocardiographic evidence of left ventricular hypertrophy[6-9]. Echocardiography is a sensitive, non-invasive technique for estimating left ventricular mass and detecting left ventricular hypertrophy, and is useful in detecting left ventricular geometric patterns and their prognostic relevance in the general population[10-13].

Data from the Framingham Heart Study, regarding an elderly cohort of more than 1000 men and women, have documented an association between echocardiographically determined left ventricular hypertrophy and cardiovascular disease, after adjustment for traditional cardiovascular risk factors[6].

The mechanism for increased left ventricular mass in obese subjects is not clearly understood. Although hypertension, a leading cause of left ventricular hypertrophy, is frequent in obese subjects, data from the Framingham Heart Study have demonstrated that the increased left ventricular mass in obesity occurs independent of hypertension[8].
Recent reports suggest that insulin resistance and compensatory hyperinsulinaemia, closely related to obesity, may directly promote left ventricular hypertrophy by a variety of means\(^1\). The aim of this study was to establish a correlation among echocardiographic left ventricular mass, ambulatory mean blood pressure, insulin resistance, hyperinsulinaemia and adipose tissue distribution in obese, normotensive, elderly subjects.

### Subjects and Methods

#### Subjects

This study examined two groups of normotensive elderly subjects recruited from Geriatric Departments. They were well matched for age (68·5 ± 6·4 years): 29 were obese males with a body mass index >30 and 20 lean males with a body mass index <25.

Exclusion criteria were: age ≤ 60 years; a history of hypertension, systolic blood pressure >140 mmHg, or diastolic blood pressure >90 mmHg measured at either of two visits; a history or clinical–instrumental evidence of ischaemic heart disease, congestive heart failure, valvular heart disease, or chronic pulmonary disease; medication for the treatment of hypertension; a history or biochemical evidence of diabetes mellitus, or impaired glucose tolerance; treatment with any medication known to affect left ventricular mass or glucose tolerance (beta-blockers, vasodilatators, thiazide diuretics, calcium antagonists, angiotensin converting enzyme inhibitors and corticosteroids).

All subjects had a stable weight, with a variability <5% for the preceding year. None were involved in a regular exercise programme or had limitations in their daily activities. To be eligible for this study, subjects underwent a clinical interview and a detailed physical examination by two physicians in the two following days.

Of the first 54 obese responders, the following were excluded: six with ischaemic heart disease, eight with hypertension, three with valvular heart disease and eight with diabetes mellitus or impaired glucose tolerance at oral glucose tolerance test.

The 29 obese and the 20 lean subjects, who met the above criteria, underwent, on the same day, detailed echocardiography and 24-h non-invasive ambulatory blood pressure monitoring. Two days later, they underwent an oral glucose tolerance test and evaluation of adipose tissue distribution using anthropometric and ultrasound measurements. All these patients were found to be healthy and normotensive, with a normal glucose tolerance test. The study protocol was in accordance with The Second Declaration of Helsinki and approved by the Ethics Committee on Human Research at the University of Rome. Informed written consent was obtained from all subjects.

#### Methods

A mercury column sphygmonanometer was used, after 10 min rest in the supine position, to measure arterial blood pressure in the left arm, taking into account the first and fifth phases of the Korotko sounds. A large cuff was used in obese patients.

The 24-h blood pressure recordings were obtained with a commercially available, non-invasive ambulatory blood pressure recorder (A & D TM 2420/21)\(^1\). The recorder was set to take readings at 15 min intervals from 6:00 to 23:00, and at 20 min intervals from 23:00 to 6:00. Subjects were allowed to follow their normal daily routine during pressure recordings. Each time a reading was taken, subjects were instructed to remain motionless and to record their activity on a diary sheet. The tapes were analysed on a Kontron Cardio 80 CP/M computer (Kontron Instruments, Everett, MA, U.S.A.).

The recorder automatically discarded artifactual readings; furthermore, during computer analysis, additional readings were rejected if the pulse pressure was less than 20 mmHg, the diastolic blood pressure less than 50 mmHg, or the systolic blood pressure more than 260 mmHg in isolated readings. All recordings were included in the study, except for 85% of the maximal number of 84 readings which exceeded the deletion criteria during the 24 h. Only three subjects were required to repeat the ambulatory blood pressure recording.

From the 24-h blood pressure profiles, we calculated the following values: 24-h mean systolic blood pressure, 24-h mean diastolic blood pressure, daytime and night-time mean systolic and diastolic values\(^2\). We considered daytime hours as being from 6:00 to 23:00 and night-time hours from 23:00 to 6:00.

All subjects were submitted to echocardiographic evaluation; M-mode tracings obtained under two-dimensional control were recorded using an ATL Ultrasound 8 mark 8 system (Advanced Technology Laboratories, Bellevue, Washington, U.S.A.) with an ATL 3·00 MHz transducer\(^1\). The subjects were studied in the morning, after at least 30 min of supine rest, in the left lateral decubitus position. All echocardiographic tracings were coded, digitized with a hand-controlled crosswire cursor and calculated in a blind manner by two experienced physicians using a computerized method of analysis. The mean value obtained from at least five left ventricular measurements per observer was computed to reduce to a minimum intra- and inter-observer variability.

The left ventricular mass (LVM) was calculated by measuring the end-diastolic left ventricular internal diameter (LVID), the interventricular septum thickness (IVST) and the posterior wall thickness (PWT), according to the Penn Convention. The formula of Devereux and Reichek\(^1\) was used:

\[
LVM \ (g) = 1.04 \times [LVID + IVST + PWT]^3 - (LVID)^3 - 13.6
\]
The left ventricular mass was corrected for height to its allometric power (height$^{-2.7}$) as previously described$^{[18]}$. The relative wall thickness (RWT) was computed as $2 \times \text{PWT/LVID}$ according to Penn convention measurements$^{[19]}$.

Ultrasonic measurements of adipose tissue distribution were performed by the same operator using a Pimedical AU 920 scanner (Sweden). The subject was placed in a recumbent position, keeping his heels, buttocks and shoulders in contact with the table. Ultrasound subcutaneous adipose tissue and visceral adipose tissue were both measured next to the umbilicus in the xypho-umbilical line, as previously described$^{[20]}$. Subcutaneous and intra-abdominal fat thickness were measured using a 7.5-M Hz and a 3.5-M Hz transducer, respectively.

Weight (kg) and height (m) were measured conventionally; body mass index (kg·m$^{-2}$) and waist to hip circumference were calculated and used, respectively, as an index of obesity and of centripetal adipose tissue distribution$^{[21]}$. Hyperinsulinaemia and insulin resistance were evaluated by the insulin and glucose response to the oral glucose tolerance test. All subjects were instructed to adhere to a diet rich in carbohydrates (at least 250 g daily) and to refrain from extreme physical exercise or inactivity for at least 5 days before the investigation; they were given the 75-g oral glucose tolerance test after an overnight fast (10 to 12 h)$^{[22]}$. Blood samples were collected using EDTA and Trasylol (Miles, Rexdale, Ontario, Canada) through a venous catheter from an antecubital vein at $-15, 0, 30, 60, 90, 120, 150, 180$ min for the determination of both plasma glucose, by the enzymatic method$^{[23]}$, and insulin concentration, by radioimmunoassay$^{[24]}$.

Plasma glucose responses to the oral glucose tolerance test were interpreted according to the National Diabetes Data Group criteria$^{[22]}$. Diabetic or glucose-intolerant subjects were excluded from the study. The glycaemic and insulinemic values obtained from the oral glucose intolerance test were also used to compute the areas under glycaemic and insulinemic curves with H alf n e r’s formula, while insulin resistance was evaluated indirectly by the fasting glycaemic/insulin plasmatic levels ratio (G/I Ratio), as previously described$^{[25,26]}$.

Statistical analysis was conducted using EPI-INFO 5 statistical software on an IBM AT3 personal computer, with a conventional Student’s unpaired t-test and linear regression analysis. Summary data are shown as mean ± 1 SD. The statistical significance of the differences between obese and lean elderly subjects was assessed by student’s unpaired t-test. Linear univariate regression analysis was used to estimate the strength of association, whether between left ventricular mass and the following variables: body mass index, visceral adipose tissue distribution, waist/hip ratio, indices of insulin resistance, hyperinsulinaemia, mean blood pressure, or among hyperinsulinaemism, indices of insulin resistance and visceral adipose tissue, waist to hip ratio circumference, body mass index.

The limit of statistical significance was settled at $P < 0.05$. A stepwise multiple regression analysis, with inclusion at the 0.01 level and exclusion at the 0.05 level was used to evaluate the influence of body mass index and hyperinsulinaemia on echocardiographically determined left ventricular mass indices.

**Results**

The study population consisted of 49 elderly, normoten- sive males (29 obese and 20 lean), with no significant difference between obese and lean subjects with respect to age (mean value: $68.5 ± 6.4$ years; from 62 to 84).

The clinical, metabolic, anthropometric, and echocardiographic characteristics of the two study groups and the statistical differences are presented in Table 1. In spite of the fact that statistical analysis showed a higher, but not significant, systolic and diastolic mean blood pressure in lean as compared with obese subjects, probably due to chance, we found a significant difference ($P < 0.0001$) between the two groups, when evaluating left ventricular mass (g·m$^{-2.7}$) and the left ventricular mass index (g·m$^{-2}$); this may have been because of the myocardial hypertrophy in obese subjects.

The left ventricular internal diameter was larger, and the septal interventricular thickness and posterior wall thickness were greater in obese normotensive subjects, but no difference existed between obese and non-obese subjects in relative wall thickness, in accordance with previous reports$^{[27]}$. Visceral adipose tissue distribution and the waist/hip ratio were significantly higher in obese than in lean subjects ($P < 0.0001$). The area under the glucose curve was not statistically different in two groups, while the area under the insulin curve was higher in obese than in lean subjects ($P < 0.0001$). Similar differences were obtained in two groups when comparing fasting insulin plasmatic levels and body mass index.

Linear regression analysis was performed to define the correlation either between the left ventricular mass, the body mass index, visceral adipose tissue distribution, the waist/hip ratio, the area under the insulin curve after the oral glucose tolerance test, the G/I ratio and mean blood pressure, or between the area under the insulin curve, the G/I ratio, the body mass index, the waist to hip ratio circumference and the visceral adipose tissue (Tables 2 and 3).

All values reported herein for left ventricular mass have been normalized for height to its allometric power (height$^{-2.7}$) according to previous reports$^{[18]}$. Left ventricular mass was strongly correlated with basal plasmatic insulin levels, the area under insulin curve, the G/I ratio, intra-abdominal adipose tissue and the waist to hip ratio, and less closely with the body mass index (Table 2). No significant correlation was found between left ventricular mass, systolic or diastolic blood pressure.

The area under the insulin curve and the lower G/I ratio were closely correlated to visceral adipose tissue distribution (respectively: $P = 0.0001$; $P = 0.003$).
and to the waist/hip ratio (respectively: $P = 0.001$; $P = 0.005$), while both were very weakly correlated to body mass index ($P = n.s.$) (Table 3). The results of multiple regression analysis showed that hyperinsulinaemia in obese subjects was significantly associated with left ventricular mass, independent of body mass index values, while this correlation did not reach statistical significance in controls, even if it showed a similar tendency (Table 4).

**Discussion**

This study demonstrates, in agreement with the Cardiovascular Heart Study[28], that obesity is significantly correlated with increased left ventricular mass, independent of hypertension, particularly in elderly subjects (Table 1).

Previously, several investigators have compared significantly obese and lean subjects with regard to cardiac structure. Messerli and colleagues[29] reported an echocardiographic case-comparison study involving 17 obese normotensive subjects who were matched with identical numbers of lean normotensive subjects. The obese subjects had a greater left ventricular mass ($P < 0.001$) compared with the lean subjects. In 1988, Hammond and colleagues[27], in a study involving 162 normotensive and 462 hypertensive subjects, found that the body mass index was a significant, independent, predictor of left ventricular mass after controlling for blood pressure, gender and age in the normotensive population ($P = 0.0001$).

Furthermore, Himeno and colleagues reported that weight reduction was correlated with lower left ventricular mass, regardless of blood pressure level, in a randomized controlled trial involving obese normotensive and hypertensive subjects over 3 months[30].

The present study extends the current understanding of the relationship between obesity and left ventricular geometry. Our data suggest that hyperinsulinaemia is a better left ventricular hypertrophy

---

**Table 1** Correlations between obese and lean subjects

<table>
<thead>
<tr>
<th></th>
<th>Obese subjects</th>
<th>Lean subjects</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.21 ± 5.27</td>
<td>69.40 ± 6.70</td>
<td>n.s.</td>
</tr>
<tr>
<td>BMI (kg m$^{-2}$)</td>
<td>34.60 ± 2.92</td>
<td>23.40 ± 2.31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVMI (g)</td>
<td>203.72 ± 26.13</td>
<td>167.94 ± 18.67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVID (mm)</td>
<td>51.32 ± 4.51</td>
<td>49.73 ± 5.12</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>ISVT (mm)</td>
<td>10.39 ± 1.93</td>
<td>8.82 ± 1.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PWT (mm)</td>
<td>10.08 ± 1.91</td>
<td>8.92 ± 1.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RWT</td>
<td>0.38 ± 0.09</td>
<td>0.37 ± 0.06</td>
<td>n.s.</td>
</tr>
<tr>
<td>LVM (g m$^{-2}$)</td>
<td>48.76 ± 3.28</td>
<td>39.9 ± 2.78</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>WHR</td>
<td>1.03 ± 0.04</td>
<td>0.88 ± 0.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VAT (mm)</td>
<td>39.38 ± 6.17</td>
<td>19.60 ± 5.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulinaemic area (µU ml$^{-1}$)</td>
<td>178.70 ± 34.51</td>
<td>104.27 ± 23.71</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glycaemic area (µU ml$^{-1}$)</td>
<td>218.36 ± 38.10</td>
<td>212.11 ± 22.50</td>
<td>n.s.</td>
</tr>
<tr>
<td>Fasting insulin (µU ml$^{-1}$)</td>
<td>14.58 ± 4.47</td>
<td>8.21 ± 3.10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>G/I ratio</td>
<td>5.84 ± 2.54</td>
<td>12.14 ± 4.70</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MBP systolic (mmHg)</td>
<td>129.40 ± 14.36</td>
<td>131.74 ± 11.43</td>
<td>n.s.</td>
</tr>
<tr>
<td>MBP diastolic (mmHg)</td>
<td>81.72 ± 6.74</td>
<td>62.56 ± 4.49</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

BMI = body mass index; LVMI = left ventricular mass; LVID = left ventricular internal diameter; ISVT = interventricular septal thickness; PWT = posterior wall thickness; RWT = right wall thickness; WHR = waist:hip ratio; VAT = visceral adipose tissue; MBP = mean blood pressure.

**Table 2** Univariate correlates of left ventricular mass/height$^{2-7}$

<table>
<thead>
<tr>
<th></th>
<th>$r$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg m²)</td>
<td>0.438****</td>
<td></td>
</tr>
<tr>
<td>Fasting insulin (mcU ml$^{-1}$)</td>
<td>0.516***</td>
<td></td>
</tr>
<tr>
<td>Insulinaemic area (mcU ml$^{-1}$)</td>
<td>0.615*</td>
<td></td>
</tr>
<tr>
<td>G/I ratio</td>
<td>-0.591*</td>
<td></td>
</tr>
<tr>
<td>MBP systolic (mmHg)</td>
<td>0.194</td>
<td></td>
</tr>
<tr>
<td>MBP diastolic (mmHg)</td>
<td>0.121</td>
<td></td>
</tr>
<tr>
<td>VAT (mm)</td>
<td>0.607*</td>
<td></td>
</tr>
<tr>
<td>WHR</td>
<td>0.576**</td>
<td></td>
</tr>
</tbody>
</table>

Statistical significance *$P<0.0001$; **$P<0.001$; ***$P<0.005$; ****$P<0.05$. Abbreviations as in Table 1.

**Table 3** Correlation between insulin resistance, hyperinsulinaemia and centripetal adipose tissue distribution

<table>
<thead>
<tr>
<th></th>
<th>$r$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulinaemic area vs VAT</td>
<td>0.632</td>
<td>0.0001</td>
</tr>
<tr>
<td>Insulinaemic area vs WHR</td>
<td>0.571</td>
<td>0.001</td>
</tr>
<tr>
<td>Insulinaemic area vs BMI</td>
<td>0.338</td>
<td>0.09</td>
</tr>
<tr>
<td>G/I ratio vs VAT</td>
<td>-0.553</td>
<td>0.003</td>
</tr>
<tr>
<td>G/I ratio vs WHR</td>
<td>0.502</td>
<td>0.005</td>
</tr>
<tr>
<td>G/I ratio vs BMI</td>
<td>-0.264</td>
<td>0.113</td>
</tr>
</tbody>
</table>
indicator than body mass index (Tables 2 and 4); moreover, insulin resistance and an ensuing hyperinsulinaemic state are closely correlated with centripetal adipose tissue distribution (waist to hip ratio circumference and visceral adipose tissue) (Table 3).

The link between increased left ventricular mass and insulin resistance-hyperinsulinaemia has been previously described in several rare genetic disorders such as leprechaunism\cite{31} and total lipodystrophy\cite{32} as well as in other, more common, endocrine diseases such as hypothyroidism\cite{33}, acromegaly\cite{34}, and in infants of diabetic mothers (due to intra-uterine hyperinsulinaemia)\cite{35} or in hypertension\cite{36}. The findings of our study extend the link between hyperinsulinaemia left ventricular mass and obesity in relation to centripetal adipose tissue distribution.

Hyperinsulinaemia can induce left ventricular hypertrophy through its growth-stimulating effect\cite{37}. Insulin indeed may carry out its growth action by binding both the insulin receptors and IGF-1 receptors by reason of its structural similarity to the IGF-1 polypeptide\cite{38}. A stimulation of the IGF-1 receptors by insulin has been demonstrated in hyperinsulinaemia. This was correlated with increased DNA synthesis and cell proliferation, leading to hypertrophy of the cardiomyocytes by increasing mRNA levels in myocyte-specific genes (\(\alpha\)-actin, troponin I and myosin light chain 2) and stimulating protein synthesis\cite{39}.

A second pathway by which hyperinsulinaemia can lead to increased left ventricular mass, in obese subjects, is by the alteration of several sodium cellular transport systems. Indeed, hyperinsulinaemia is correlated with increased Na-\(\text{H}\) countertransport, across the membrane bilayer, leading to increased intracellular pH and sodium\cite{40}. The enhanced sodium concentration inhibits the Na-\(\text{Ca}\) countertransport, allowing an increase in intracellular calcium, that promotes, in association with cytoplasmatic alkalinization, the initiation of myocardial hypertrophy. The increased intracellular pH stimulates protein synthesis and cellular growth, while the enhanced intracellular calcium concentration causes the expression in cardiomyocytes of the following proto-oncogenes: c-myc, c-fos, c-Ha-ras, that represent the molecular onset of left ventricular mass hypertrophy\cite{41,42}. A further pathway by which hyperinsulinaemia can promote left ventricular hypertrophy in obese subjects is by increasing blood volume\cite{43}, through its effect on sodium reabsorption in the kidney. The increased Na-\(\text{H}\) countertransport across the basal membrane of cells in the proximal tubule or cortical thick ascending limb of Henle would promote a defect in renal salt excretion\cite{44}. This may also be due to an indirect renal effect of insulin through activation of the sympathetic nervous system\cite{45}, or impairment of atrial natriuretic peptide activity\cite{46}. The enhanced sodium reabsorption justifies the increased blood volume and cardiac output demonstrated in obese subjects\cite{47}.

All these changes, in the long run, may lead to an adaptive increase in left ventricular mass. In conclusion, our data suggest that in elderly obese subjects hyperinsulinaemia, associated with visceral adipose tissue distribution, could be considered a better indicator of left ventricular hypertrophy than body mass index. Nevertheless, further studies are necessary to clarify the strength of this correlation.

### References

Hyperinsulinemia, LV mass in the elderly obese


[40] M erban E, Koretzune Y. Cell calcium, oncogenes and hyper-