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Blood Pressure-Independent Relations of Left Ventricular Geometry to the Metabolic Syndrome and Insulin Resistance: A Population-Based Study

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Running title: LV geometry and the metabolic syndrome

Keywords: Insulin resistance, metabolic syndrome, left ventricular hypertrophy, epidemiology, population

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Abstract

Objective
Insulin resistance independently predicts heart failure and coronary disease, and has been related to thick left ventricular walls, mainly in studies of hypertensive samples not fully accounting for the influence of blood pressure. We investigated if the metabolic syndrome and insulin resistance are related to left ventricular geometry independently of blood pressure.

Design
Cross-sectional study.

Setting
A community-based sample of 820 seventy-year-old men and women (the Prospective Investigation of the Vasculature in Uppsala Seniors, PIVUS) free from valvular disease, heart failure and myocardial infarction.

Main Outcome Measures
Relations of the National Cholesterol Education Program-defined metabolic syndrome and homeostasis model assessment of insulin resistance (HOMA-IR) to echocardiographic left ventricular geometry. Models were adjusted for sex, height, intra-arterial systolic and diastolic blood pressures, and antihypertensive medication.

Results
Left ventricular mass index was increased in persons with the metabolic syndrome in the total sample (49.7 [13.1] vs. 39.7 [11.5] g/m², p<0.0001) and in subgroups of normotensive and hypertensive persons; mainly accounted for by an increased relative wall thickness. HOMA-IR was related to left ventricular mass index in the total sample (r=0.31; p<0.0001) and in hypertensive persons, but borderline significantly in normotensive persons. HOMA-IR was related to relative wall thickness in the total sample (r=0.27; p<0.001), in normotensive and hypertensive persons.

Conclusions
Left ventricular mass and relative wall thickness were increased in persons with the metabolic syndrome and were related to HOMA-IR in a large population-based sample of men and women of the same age, accounting for covariates including intra-arterial blood pressure levels.
Introduction

Insulin resistance (determined using the euglycemic insulin clamp) is an independent predictor of heart failure and coronary heart disease in the community,[1 2] and has been related to increased left ventricular wall thickness in a population-based sample.[3] The National Cholesterol Education Program (NCEP) definition of the metabolic syndrome[4] is a clinically feasible proxy for insulin resistance which facilitates the study of the adverse cardiac effects of insulin resistance, a critical issue considering the current obesity epidemic.[5]

The relations of clamp-determined insulin resistance[6 7 8 9 10] or the NCEP-defined metabolic syndrome[11 12 13] to left ventricular geometry have previously mainly been studied in limited samples of hypertensive patients, sometimes even in hypertensive patients with left ventricular hypertrophy.[10] As hypertensive patients are more insulin resistant and have more left ventricular hypertrophy than the general population, these studies have by design excluded large parts of the spectra of insulin sensitivity and left ventricular mass; and have consequently not contributed to the understanding of the relations of these parameters in the general population (or in normotensive persons, in which blood pressure-independent prohypertrophic mechanisms are more likely to be important). Furthermore, blood pressure level is one of the most important determinants of left ventricular mass, and as previous population-based studies have generally not accounted fully for blood pressure levels,[3 14] (although a few studies in hypertensive samples have adjusted for 24-hour systolic blood pressure levels[15 16]) described relations of insulin resistance or the metabolic syndrome to left ventricular geometry in the population are likely to be confounded by the effects of blood pressure. Assessments of the true relations of glucometabolic disturbances and left ventricular geometry should therefore ideally be performed in general population-based or normotensive samples rather than in hypertensive samples, and should take proper account of blood pressure levels.

We hypothesized that insulin resistance is related to altered left ventricular geometry (more specifically, to increased left ventricular wall thickness) independently of blood pressure. Accordingly, we investigated the relations of the NCEP-defined metabolic syndrome and homeostasis model assessment-insulin resistance (HOMA-IR) to echocardiographic left ventricular geometry in a large population-based sample of men and women of the same age with emphasis on subgroup analyses in normotensive participants and adjustment for intra-arterial blood pressure levels and antihypertensive medication. Intra-arterial measurements are the gold standard of blood pressure measurement, which noninvasive modes of measurement, such as sphygmomanometers and oscillatory devices, strive to approximate.
Methods

Study Sample
Men and women living in the community of Uppsala, Sweden, were chosen from the community register and were in a randomised order invited by letter within two months after their 70th birthday to the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS).[17] Of 2025 invited persons, 1016 (50%) participated (51% women). For the present study, we excluded participants with significant echocardiographic valvular disease (n=28), a self-reported history of myocardial infarction (n=69) or heart failure (n=18), or incomplete echocardiographic data (n=81). This left 820 participants (53% women) eligible for the present study. All analyses were performed in the total sample and separately in one normotensive (n=249) and one hypertensive (n=571) stratum, in order to account as well as possible for the effects of high blood pressure on left ventricular geometry and function. In secondary analyses, all models were stratified by quartiles of intra-arterial systolic blood pressure. The Ethics Committee of Uppsala University approved the study and the participants gave informed consent. Because of the low participation rate, 100 consecutive non-participants of the main study were evaluated using a questionnaire. Prevalences of cardiovascular drug intake and ischemic heart disease were similar in participants and non-participants, whereas the prevalences of diabetes, congestive heart failure and stroke appeared higher among non-participants.[17]

Clinical and Laboratory Investigations
Prior to their clinical examination, subjects completed a questionnaire concerning their medical history, regular medication use, smoking habits and physical activity (times /week devoted to >=30 minutes of mild exercise [e.g. walks, cycling, golf, gardening] or heavy exercise [e.g. running, swimming, playing tennis or football]). All subjects were investigated in the morning after an overnight fast and no medication was taken on the day of the investigation. Anthropometric measures were collected and blood samples were taken and analyzed by standard laboratory techniques. Hypertension was defined as non-invasively measured supine systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg, and/or current use of anti-hypertensive medication. Of the latter, 51% used beta-blockers, 34% calcium antagonists, 33% diuretics, 22% angiotensin-converting enzyme inhibitors, and 26% used angiotensin receptor blockers, in monotherapy or in combination. Impaired fasting glucose (fasting glucose 5.6-6.9 mmol/l) and diabetes (fasting glucose ≥7.0 or treatment with insulin or oral antidiabetic drugs) were defined according to current criteria.[18] Serum insulin was measured by an enzymatic-immunological assay (Boehringer Mannheim). HOMA-IR was defined using fasting plasma glucose and insulin concentrations by the formula: fasting insulin*fasting glucose/22.5.[19] The metabolic syndrome was defined according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III[4] with a minor modification, using the non-invasively measured blood pressures (Table 1). The intra-arterial blood pressure recordings were obtained by a catheter (20G/1.10 mm x 45 mm) in the brachial artery connected to a pressure tube (150 mm) and a transducer (DTX Plus Transducer DT-XX). Systolic and diastolic blood pressures were continuously recorded for five minutes and the mean values during this period were used for the analyses. The recording was performed in the supine position at least 30 min following the arterial catheterization.
Table 1. The National Cholesterol Education Program Definition of the Metabolic Syndrome

<table>
<thead>
<tr>
<th>MetS hyperglycemia</th>
<th>Fasting p-glucose $\geq 6.1$ mmol/l or Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>MetS high blood pressure</td>
<td>Blood pressure $\geq 130/85$ mmHg or Rx</td>
</tr>
<tr>
<td>MetS high triglycerides</td>
<td>Fasting triglycerides $\geq 1.7$ mmol/l</td>
</tr>
<tr>
<td>MetS low HDL-cholesterol</td>
<td>HDL-cholesterol $&lt; 1.04$ mmol/l (men) or $&lt; 1.30$ mmol/l (women)</td>
</tr>
<tr>
<td>MetS abdominal obesity</td>
<td>Waist circumference $&gt; 102$ cm (men) or $&gt; 88$ cm (women)</td>
</tr>
</tbody>
</table>

The MetS hyperglycemia criterion was modified from the original definition to include pharmacological treatment with insulin or oral antidiabetic drugs. MetS, metabolic syndrome; Rx, pharmacological treatment.

Echocardiography and Doppler

A comprehensive two-dimensional and Doppler echocardiography was performed with an Acuson XP124 cardiac ultrasound unit (Acuson, California, USA). A 2.5 MHz transducer was used for the majority of the examinations. The echocardiograms were performed approximately one week after the main examination. The echocardiographer (Dr Lind) was blinded to the clinical data. Presence of stenosis or regurgitations in the mitral and aortic valves was recorded by use of color and continuous Doppler. Left ventricular dimensions were measured with M-mode on-line from parasternal projections, using a leading-edge to leading-edge convention. Measurements included left atrial diameter (LA), interventricular septal thickness (IVS), left ventricular posterior wall thickness (PW), left ventricular diameter in end diastole and end systole (LVEDD, LVESD). Left ventricular wall thickness was calculated as IVS+PW; relative wall thickness (RWT) as (IVS+PW)/LVEDD; and left ventricular mass LVM = $0.8 \times (1.04 \times ([IVS+LVEDD+PW]^3-LVEDD^3)+0.6$ g [20]. Left ventricular mass index (LVMI) was obtained by indexing LVM to height $^{2.7}$ [21].

Statistical Analysis

We initially investigated distributional properties of all variables, and non-normally distributed ones were logarithmically transformed. All analyses were performed in the total sample, and separately in the normotensive and hypertensive strata, as well as in the four quartiles of intra-arterial systolic blood pressure. Analysis of covariance was used to compare levels of echocardiographic variables (LVMI, LVM, LVWT, LVEDD and RWT) between persons with vs. without the metabolic syndrome, adjusting for sex, height, intra-arterial systolic and diastolic blood pressures, and use of antihypertensive medication, except for the LVMI models, which were adjusted for all of these but height. Linear regression models were used (Pearson’s correlation coefficients reported) to investigate the relations of HOMA-IR to LVM and RWT, adjusting for the same above-mentioned covariates. Interaction terms between sex and the metabolic syndrome or HOMA-IR were tested in all models; as well as three interaction terms between the metabolic syndrome and intra-arterial systolic and diastolic blood pressure and non-invasive hypertension status, and three interaction terms between HOMA-IR and intra-arterial pressures and hypertension status, in all corresponding models. Stata 9.2 (StataCorp, College Station) was used for all analyses. Two-sided significance tests were used, with p<0.05 considered statistically significant.

In secondary analyses, all models in the total sample were adjusted additionally for mild and heavy exercise, and in another set of models additionally for glucose and insulin levels.
Results

The metabolic syndrome was present in 20% of the sample (19% of men, 22% of women). Baseline characteristics are presented in Table 2.

Left ventricular mass index was increased in persons with the metabolic syndrome, in the total sample as well as in both the normotensive and hypertensive strata, independently of covariates including intra-arterial systolic and diastolic blood pressures and use of antihypertensive medication (Table 3). This increased mass was mainly accounted for by an increased left ventricular wall thickness, and less by an increased inner diameter (Table 3). Consequently, left ventricular relative wall thickness was increased in persons with the metabolic syndrome (Table 3).

HOMA-IR was related to left ventricular mass index in the total sample (Figure 1) and in hypertensive persons \( r=0.32; p<0.0001 \), but borderline significantly in normotensive persons \( r=0.16; p=0.06 \), adjusting for covariates. HOMA-IR was also related to left ventricular relative wall thickness in the total sample (Figure 2), as well as in hypertensive \( r=0.23; p<0.0001 \) and normotensive persons \( r=0.26; p=0.003 \). The relations of HOMA-IR to left ventricular mass index and relative wall thickness were slightly lower than the relations of intra-arterial systolic and diastolic blood pressures to left ventricular mass index \( r=0.33-0.39 \), but of similar magnitude as the relations of the blood pressures to relative wall thickness \( r=0.24-0.29 \).

Repeating all analyses by quartiles of intra-arterial systolic blood pressure (Table 4), most of the observations (especially regarding left ventricular wall thickness) were consistent across the four strata.

Interaction terms between sex and the metabolic syndrome or HOMA-IR were not significant in any model. In models with left ventricular mass as dependent variable, interaction terms between hypertension status and HOMA-IR and between hypertension status and the metabolic syndrome were statistically significant \( p<0.0001 \) and \( p=0.047 \), respectively. No other interactions analyzed were statistically significant.

In secondary analyses adjusting additionally for mild and heavy exercise, results were very similar to those in the primary analyses (illustrated by relations of HOMA-IR to left ventricular mass index \( r=0.32, p<0.0001 \) and relative wall thickness \( r=0.23, p<0.0001 \) in the total sample). In another set of models, adjusting additionally for glucose and insulin levels instead of exercise, all analyses of covariance remained statistically significant in the total sample except for the relative wall thickness model \( p=0.11 \).
## Table 2. Clinical and Echocardiographic Characteristics

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Total sample (n=820)</th>
<th>Normotensive (n=249)</th>
<th>Hypertensive (n=571)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women, n (%)</strong></td>
<td>431 (53)</td>
<td>117 (47)</td>
<td>314 (55)</td>
</tr>
<tr>
<td><strong>Intra-arterial systolic blood pressure, mm Hg</strong></td>
<td>146.5 (20.0)</td>
<td>126.8 (10.4)</td>
<td>155.4 (16.7)</td>
</tr>
<tr>
<td><strong>Intra-arterial diastolic blood pressure, mm Hg</strong></td>
<td>68.6 (9.2)</td>
<td>62.6 (7.2)</td>
<td>71.6 (8.6)</td>
</tr>
<tr>
<td><strong>Non-invasive systolic blood pressure, mm Hg</strong></td>
<td>149.6 (22.6)</td>
<td>125.3 (9.8)</td>
<td>160.1 (18.1)</td>
</tr>
<tr>
<td><strong>Non-invasive diastolic blood pressure, mm Hg</strong></td>
<td>78.8 (10.2)</td>
<td>71.2 (8.0)</td>
<td>82.0 (9.3)</td>
</tr>
<tr>
<td><strong>Antihypertensive medication, n (%)</strong></td>
<td>227 (28)</td>
<td>0</td>
<td>227 (40)</td>
</tr>
<tr>
<td><strong>Fasting triglycerides, mmol/l</strong></td>
<td>1.11 (0.62)</td>
<td>1.02 (0.54)</td>
<td>1.17 (0.67)</td>
</tr>
<tr>
<td><strong>HDL-cholesterol, mmol/l</strong></td>
<td>1.54 (0.43)</td>
<td>1.55 (0.46)</td>
<td>1.53 (0.42)</td>
</tr>
<tr>
<td><strong>Lipid-lowering medication, n(%)</strong></td>
<td>102 (12)</td>
<td>19 (8)</td>
<td>83 (15)</td>
</tr>
<tr>
<td><strong>Body mass index, g/m²</strong></td>
<td>26.7 (4.0)</td>
<td>25.5 (3.6)</td>
<td>27.3 (4.0)</td>
</tr>
<tr>
<td><strong>Waist circumference, cm</strong></td>
<td>90.2 (11.0)</td>
<td>88.2 (10.6)</td>
<td>91.1 (11.0)</td>
</tr>
<tr>
<td><strong>Fasting p-glucose, mmol/l</strong></td>
<td>5.6 (0.9)</td>
<td>5.4 (0.7)</td>
<td>5.6 (0.9)</td>
</tr>
<tr>
<td><strong>Fasting insulin, mU/l</strong></td>
<td>7.3 (5.3)</td>
<td>6.8 (5.4)</td>
<td>7.6 (5.3)</td>
</tr>
<tr>
<td><strong>HOMA-IR</strong></td>
<td>1.6 (1.4)</td>
<td>1.5 (1.3)</td>
<td>1.7 (1.5)</td>
</tr>
<tr>
<td><strong>Anti-diabetic medication, n(%)</strong></td>
<td>43 (5)</td>
<td>8 (3)</td>
<td>35 (6)</td>
</tr>
<tr>
<td><strong>Diabetes, n(%)</strong></td>
<td>75 (9)</td>
<td>16 (6)</td>
<td>59 (10)</td>
</tr>
<tr>
<td><strong>Impaired fasting glucose, n(%)</strong></td>
<td>283 (35)</td>
<td>81 (33)</td>
<td>202 (36)</td>
</tr>
<tr>
<td><strong>Heavy exercise, times/week</strong></td>
<td>0 (1)</td>
<td>0 (1)</td>
<td>0 (1)</td>
</tr>
<tr>
<td><strong>Mild exercise, times/week</strong></td>
<td>4 (4)</td>
<td>4 (4)</td>
<td>4 (4)</td>
</tr>
<tr>
<td><strong>NCEP MetS, n (%)</strong></td>
<td>168 (20)</td>
<td>21 (8)</td>
<td>147 (26)</td>
</tr>
<tr>
<td><strong>MetS hyperglycemia, n (%)</strong></td>
<td>183 (22)</td>
<td>46 (18)</td>
<td>137 (24)</td>
</tr>
<tr>
<td><strong>MetS high blood pressure, n (%)</strong></td>
<td>673 (82)</td>
<td>102 (41)</td>
<td>571 (100)</td>
</tr>
<tr>
<td><strong>MetS high triglycerides, n (%)</strong></td>
<td>129 (16)</td>
<td>23 (9)</td>
<td>106 (19)</td>
</tr>
<tr>
<td><strong>MetS low HDL-cholesterol, n (%)</strong></td>
<td>121 (15)</td>
<td>30 (12)</td>
<td>91 (16)</td>
</tr>
<tr>
<td><strong>MetS abdominal obesity, n (%)</strong></td>
<td>263 (32)</td>
<td>58 (23)</td>
<td>205 (36)</td>
</tr>
</tbody>
</table>

## Echocardiographic Characteristics

<p>| LV mass index (g/m²) | 41.8 (12.5) | 34.3 (9.1) | 45.1 (12.4) |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass (g)</td>
<td>172.6 (56.6)</td>
<td>145.2 (42.2)</td>
<td>184.6 (58.0)</td>
</tr>
<tr>
<td>LV wall thickness (mm)</td>
<td>20.5 (3.5)</td>
<td>18.5 (2.9)</td>
<td>21.3 (3.4)</td>
</tr>
<tr>
<td>LV end-diastolic diameter (mm)</td>
<td>46.7 (5.3)</td>
<td>45.8 (4.9)</td>
<td>47.1 (5.4)</td>
</tr>
<tr>
<td>LV relative wall thickness</td>
<td>0.44 (0.09)</td>
<td>0.41 (0.07)</td>
<td>0.46 (0.09)</td>
</tr>
</tbody>
</table>

Data are n (%), means (standard deviations), or medians (interquartile ranges); the latter for skewed variables (HOMA-IR, triglycerides, insulin, glucose, and exercise variables). HOMA-IR, homeostasis model assessment-insulin resistance; NCEP, National Cholesterol Education Program; MetS, metabolic syndrome; LV, left ventricular.
Table 3. Echocardiographic Characteristics by Presence versus Absence of the Metabolic Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Total sample (n=820)</th>
<th>Normotensive (n=249)</th>
<th>Hypertensive (n=571)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MetS present</td>
<td>MetS absent</td>
<td>p</td>
</tr>
<tr>
<td>LV mass index (g/m².7)</td>
<td>49.7 (13.1)</td>
<td>39.7 (11.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>205.0 (60.5)</td>
<td>164.3 (52.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV wall thickness (mm)</td>
<td>22.6 (3.3)</td>
<td>19.9 (3.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV end-diastolic diameter (mm)</td>
<td>47.8 (5.6)</td>
<td>46.4 (5.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>LV relative wall thickness</td>
<td>0.48 (0.09)</td>
<td>0.43 (0.08)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are means (standard deviations) and analyses of covariance p-values. Analyses of covariance are adjusted for sex, height, intra-arterial systolic and diastolic blood pressures, and antihypertensive medication, except for the analyses of LV mass index, which are adjusted for all of these but height. MetS, National Cholesterol Education Program metabolic syndrome; LV, left ventricular.
<table>
<thead>
<tr>
<th>Quartile 1 (95-132 mm Hg)</th>
<th>Quartile 2 (133-145 mm Hg)</th>
<th>Quartile 3 (146-160 mm Hg)</th>
<th>Quartile 4 (161-216 mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HOMA-IR</strong></td>
<td><strong>HOMA-IR</strong></td>
<td><strong>HOMA-IR</strong></td>
<td><strong>HOMA-IR</strong></td>
</tr>
<tr>
<td>r</td>
<td>p</td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>LV mass index</td>
<td>0.24 0.01</td>
<td>0.14 0.15</td>
<td>0.43 &lt;0.0001</td>
</tr>
<tr>
<td>LV mass</td>
<td>0.24 0.02</td>
<td>0.20 0.09</td>
<td>0.49 &lt;0.0001</td>
</tr>
<tr>
<td>LV wall thickness</td>
<td>0.29 0.003</td>
<td>0.36 &lt;0.0001</td>
<td>0.50 &lt;0.0001</td>
</tr>
<tr>
<td>LV end-diastolic diameter</td>
<td>0.06 0.78</td>
<td>-0.09 0.04</td>
<td>0.24 0.08</td>
</tr>
<tr>
<td>LV relative wall thickness</td>
<td>0.23 0.02</td>
<td>0.38 &lt;0.0001</td>
<td>0.29 0.02</td>
</tr>
</tbody>
</table>

Data are Pearson’s correlation coefficients and corresponding p-values, and analyses of covariance p-values. All models are adjusted for sex, height, intra-arterial systolic and diastolic blood pressures, and antihypertensive medication, except for the LV mass index models, which are adjusted for all of these but height. HOMA-IR, homeostasis model assessment-insulin resistance; MetS, National Cholesterol Education Program metabolic syndrome; LV, left ventricular.
Discussion
This study demonstrates strong relations of the metabolic syndrome and HOMA-IR to left ventricular mass and relative wall thickness, independent of intra-arterial blood pressures, antihypertensive medication, and hypertension status in a large population-based sample.

Comparisons with Previous Studies
The relations in the present study of glucometabolic disturbances to mainly an increased left ventricular relative wall thickness confirm previous observations in other population-based samples,[3 14 22 23 24] but expand the knowledge as we were able to control for blood pressure to an unprecedented extent in a population-based sample. Firstly, we analyzed normotensive and hypertensive strata separately, and demonstrated relations of glucometabolic disturbances to left ventricular hypertrophy also in normotensive individuals. Secondly, we were able to adjust for intra-arterial systolic and diastolic blood pressures, and use of antihypertensive medication. To our knowledge, this is the first study to account for intra-arterial blood pressures. In a further attempt to eliminate the effects of blood pressure on the investigated relations, we repeated all models by quartiles of intra-arterial systolic blood pressure. The observed relations, especially those to left ventricular wall thickness, were remarkably consistent across these strata, considering the reduced statistical power.

In general, previous studies are difficult to compare, as they have used a variety of assessments of glucometabolic dysregulation, a variety of echocardiographic left ventricular mass and wall thickness assessments and indexations for body size, and different sets of covariates. Two previous studies of hypertensive samples[15 16] (the suboptimal population in this respect, as outlined previously) have accounted for 24-hour systolic blood pressure; whereas previous studies of general population samples (the more relevant population) have not accounted fully for blood pressure levels.[3 14]

Potential Mechanisms
Numerous plausible mechanisms exist to explain the relations of the metabolic syndrome and insulin resistance to left ventricular mass and wall thickness. Firstly, insulin may act as a growth hormone for cardiomyocytes, mainly through the extracellular signal-regulated kinase (ERK) and/or protein kinase C (PKC) pathways,[25] illustrated by an increased myocardial mass in an experimental model exposing rats to sustained hyperinsulinemia.[26] Insulin also stimulates collagen synthesis in cardiac fibroblasts.[25] Hyperinsulinemia is a frequent feature of the metabolic syndrome in non-diabetic persons. Secondly, hyperglycemia may itself promote left ventricular hypertrophy, mainly involving transforming growth factor β-1 and collagen synthesis by cardiac fibroblasts,[25] likely via the phosphatidylinositol 3-kinase[25] and PKC-β[27 28] pathways. Further, insulin interacts with neurohormonal systems and activates the sympathetic nervous system,[29] increases the pressor response to angiotensin II,[30] and increases the stimulating effects of angiotensin II on ERKs involved in cellular proliferation and extracellular matrix deposition.[31] The observed relations of the metabolic syndrome and HOMA-IR to mainly an increased left ventricular relative wall thickness in the present study support a view of the glucometabolic disturbances acting principally as growth factors for the myocardium, which would not primarily affect the left ventricular lumen size. This may be further supported by the metabolic syndrome models adjusted for glucose and insulin levels, variables in the causal pathway according to that hypothesis, in which only the relative wall thickness models lost statistical significance.
Our observations may also be partly explained by other mechanisms than those driven directly by glucose and/or insulin, such as obesity-related volume load or dyslipidemia- or inflammation-related vascular stiffness.

**Strengths and Limitations**

A limitation of the present study is the moderate participation rate. In a questionnaire answered by 100 consecutive non-participants, the main difference between participants and non-participants was a higher prevalence of a history of stroke in non-participants. Our study has an unknown generalizability to groups other than elderly Caucasians. It should be noted that very low blood pressures are unusual among the elderly, so similar investigations in younger samples of the general population are warranted to fully elucidate to what extent the observed relations are truly blood pressure-independent. Strengths of the study include the large, homogenous community-based sample of men and women of the same age (circumventing the powerful effects of age on the cardiovascular system), and the availability of intra-arterial blood pressures. Furthermore, the demonstration of consistent relations in multiple subgroups and between several measures of left ventricular hypertrophy and two measures of glucose dysregulation, using a limited number of statistical tests warranted by a succinct hypothesis, strengthens the study.

**Conclusion**

In conclusion, left ventricular mass and wall thickness were increased in persons with the NCEP-defined metabolic syndrome and were related to HOMA-IR in a large population-based sample of men and women of the same age, accounting for intra-arterial blood pressure levels. If confirmed, this may implicate that insulin resistance should be added to the short list of hemodynamic load-independent determinants of left ventricular geometry, alongside other neurohormonal factors such as components of the renin-angiotensin-aldosterone system.
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Competing Interests
All authors declare that the answer to the questions on the competing interest form bmj.com/cgi/content/full/317/7154/291/DC1 are all No and therefore have nothing to declare.

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Figure Legends
Figure 1. Relations of homeostasis model assessment-insulin resistance (HOMA-IR) to left ventricular mass index. Model adjusted for sex, intra-arterial systolic and diastolic blood pressures, and antihypertensive medication.

Figure 2. Relations of homeostasis model assessment-insulin resistance (HOMA-IR) to left ventricular relative wall thickness. Model adjusted for sex, height, intra-arterial systolic and diastolic blood pressures, and antihypertensive medication.
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Left Ventricular Relative Wall Thickness vs \( \ln(\text{HOMA-IR}) \)

- Correlation coefficient: \( r = 0.27 \)
- Statistically significant: \( p < 0.0001 \)