DETERMINANTS OF ECHOCARDIOGRAPHICALLY MEASURED LEFT VENTRICULAR MASS IN DIABETIC PATIENTS WITH OR WITHOUT SILENT MYOCARDIAL ISCHAEMIA


SUMMARY - Left ventricular hypertrophy (LVH) is a recognized independent risk factor for cardiovascular morbidity and mortality. The purpose of this study was to assess the determinants of left ventricular mass index (LVMI), according to the presence or absence of silent myocardial ischaemia (SMI), in diabetic patients with at least two additional risk factors but with no known coronary artery disease. Eighty diabetic patients (14 Type 1 and 66 Type 2) were studied, and LVMI was measured echocardiographically. Three non-invasive tests (the ECG stress test, thallium-201 myocardial scintigraphy with intravenous dipyridamole infusion, and ambulatory 48-h ECG monitoring) were performed on all patients. Forty-five percent of patients had LVH (LVMI ≥ 110 g/m² in men and ≥ 110 g/m² in women). Twenty-six patients (37%) had SMI assessed on at least one of the non-invasive tests, 7 of whom had significant coronary stenoses on angiography. LVMI was significantly higher in patients with coronary stenoses on angiography than in those with SMI but without coronary stenoses or in those without SMI (p < 0.05), and was correlated with systolic blood pressure. In patients free of SMI, LVMI correlated with creatininemia. In patients with SMI and normal coronary arteries on angiography, LVMI correlated with the waist/hip girth ratio, the log urinary albumin excretion rate and the red blood cell filtration index (an index of rigidity). This study suggests that LVH is very frequent in diabetic patients and that the main factor contributing to the increase of LVMI differs according to the presence or absence of SMI and coronary stenoses: volume load in patients free of SMI, microcirculatory disorders in those with SMI but with normal coronary arteries, and blood pressure in those with coronary stenoses.

Key-words: left ventricular mass, left ventricular hypertrophy, echocardiography, diabetes mellitus, vasculopathy, silent myocardial ischaemia.

RÉSUMÉ - Déterminants de la masse ventriculaire gauche mesurée par échographie chez des diabétiques avec ou sans ischémie myocardique silencieuse.

L’œdème ventriculaire gauche (OVG) est un facteur de risque indépendant reconnu de morbimortalité cardiovasculaire. Le but de cette étude était d’évaluer les déterminants de l’index de masse ventriculaire gauche (LVMI) selon la présence ou l’absence d’ischémie myocardique silencieuse (IMS), chez des patients diabétiques ayant au moins deux facteurs de risque supplémentaires, mais indemnes de maladie coronaire connue. Quatre-vingts diabétiques, 14 de type 1 (DID) et 66 de type 2 (DNID) ont été étudiés. LVMI a été mesuré par échocardiographie. Trois épreuves non invasives: l’épreuve d’effort, la scintigraphie myocardique au thallium-201 avec administration intraveineuse de dipyridamole et un enregistrement ECG ambulatoire pendant 48 heures, ont été effectuées chez tous les patients, Quarante-cinq pour cent des patients avaient une HVG (LVMI > 110 g/m² chez les hommes, et > 110 g/m² chez les femmes). Vingt-six patients (37%) avaient une IMS selon au moins une épreuve non invasive. Sept d’entre eux avaient des sténoses coronaires significatives à l’angiographie. Chez les patients ayant des sténoses coronaires à l’angiographie, LVMI était significativement plus grand que chez les patients avec IMS mais sans sténose coronaire, et chez les patients sans IMS (p < 0.05), et cet index était corrélé à la pression artérielle systolique. Chez les patients indemnes d’IMS, LVMI était corrélé à la créatininémie. Chez les patients avec IMS et coronaires angiographiquement normales, LVMI était corrélé au rapport de taille/taille de hanches, au log-réserve de l’excrétion urinaire d’albumine et à l’index de filtration des hématies (un index de rigidité). Cette étude suggère que 1) l’HVG est très fréquente chez les patients diabétiques, 2) le principal facteur qui peut contribuer à l’augmentation de LVMI est différent selon la présence ou l’absence d’IMS et de sténoses coronaires: - charge volumique chez les patients indemnes d’IMS, - désordres microcirculatoires chez ces patients atteints d’IMS mais ayant des coronaires angiographiquement normales, - pression artérielle chez ceux ayant des sténoses coronaires.

Mots-clés : masse ventriculaire gauche, hypertrophie ventriculaire gauche, échocardiographie, diabète sucré, maladie vasculaire, ischémie myocardique silencieuse.

(1) Department of Cardiovascular Diseases, Clinique du Vert Galant, Tremblay en France, France.
(2) Department of Endocrinology-Diabetology-Nutrition, Paris-Nord University, Jean Verdier Hospital, Bondy, France.
(3) Departments of Internal Medicine and Cardiology, and Godinot Institute, Robert Debré Hospital, Reims, France.
(4) Department of Physiology, Louis-Mourier Hospital, Colombes, France.
Increased left ventricular mass (LVM) has been shown to be an independent risk factor for both coronary heart disease events and all causes of mortality [1, 2]. Left ventricular hypertrophy (LVH) prevails in hypertensive patients. A few studies have focused on LVH in diabetic patients and its correlates with nephropathy and cardiac autonomic neuropathy [3-7]. To our knowledge, the relation between LVH and silent myocardial ischaemia (SMI) has not been extensively studied in diabetic patients. SMI in diabetic patients with no overt heart disease is as frequent as 17 to 29% [8-10]. We have recently shown that LVH is frequent among diabetic patients with SMI and coronary stenoses [10]. Thus, SMI, which has not been considered before in studies of the determinants of LVH, should be included as a possible determinant.

Rheologic disorders are frequent in diabetic patients [11, 12] and have also been reported in hypertensive patients. Moreover, whole blood viscosity has been identified as a determinant of cardiac hypertrophy in systemic hypertension [13] and might play a similar role in diabetes.

Echocardiography provides a reliable noninvasive estimation of LVM and has proved to be a more sensitive tool for the detection of LVH than other techniques previously described [14].

The purpose of this study was to examine the determinants of LVM in a diabetic population without overt heart disease, according to the presence or absence of SMI.

■ PATIENTS AND METHODS

Patients – Ninety-two consecutive diabetic patients (53 men, 39 women) without angina and with a normal 12-lead resting ECG were selected from two diabetes units. Seventy-five had non-insulin-dependent (Type 2) and 17 insulin-dependent (Type 1) diabetes. To obtain a high proportion with coronary disease, patients were selected on the basis of diabetes duration longer than 15 years for Type 1 and 5 years for Type 2 plus the presence of at least two other risk factors for atherosclerosis. The risk factors were defined as follows: hyperlipidaemia (serum total cholesterol > 6.5 mmol/l and/or triglycerides > 2.5 mmol/l and/or current treatment by lipid-lowering-drugs): 54 patients; hypertension > 140/80 mmHg (in agreement with recently published criteria [15]): 58 patients; family history of cardiovascular disease before 50 years: 26 patients; smoking habits: 47 patients; overt or incipient nephropathy (urinary albumin excretion rate > 300 mg/24 h or > 30 mg/24 h respectively): 26 patients; obesity defined by a body mass index > 29 kg/m²: 33 patients; and lower limb obstructive vascular disease confirmed by ultrasoundography: 14 patients.

Patients known to have chronic obstructive airway disease and asthma, renal impairment with creatinemia > 250 μmol/l, thyroid disease, chronic alcoholism, and a body weight above 110 kg were excluded from the study. Patients treated with beta-blockers or calcium channel blockers were included after a washout period of at least two days and replacement therapy with central antihypertensive drugs. All participants gave their written informed consent. The study design was approved by the local ethics committee.

Echocardiographic measurements – Echocardiograms were performed according to a standard protocol by skilled sonographers (one in each centre). They were obtained with the participants lying in left lateral decubitus position, with the head angled 30° from horizontal. Recordings were done using an ALOKA model SSD-870, equipped with phased-array 2.5 and 3.5 MHz transducers, and a Hewlett-Packard Sonos 5000, equipped with 2.5 and 1.9 MHz transducers. A two-dimensional parasternal long-axis view of the left ventricle was obtained to adjust the M-mode cursor position perpendicular to the interventricular septum and posterior wall of the left ventricle at the mitral valve chordae level. M-mode left ventricular measurements were obtained at end diastole. End-diastolic measurement criteria included Penn Conventional measurements [16]. Endocardial and epicardial surfaces were excluded from the measurement of wall thickness. Endocardial surfaces were included in the left ventricle dimension measurement. Diastole was defined as the peak or R wave of the QRS complex.

LVM was calculated according to the equation of Devereux and Reichek [15] using the following formula:

\[
LVM(\text{g}) = 1.04\left( \frac{IVSTd + PWTd + LVIDd}{LVIDd} \right)^3 - 13.6
\]

where IVSTd is the interventricular septal thickness at end diastole, PWTd the posterior wall thickness at end diastole, and LVIDd the left ventricle internal dimension at end diastole. The LVM index (LVMi) was calculated by dividing LVM by body surface area (g/m²). The latter was calculated according to the Dubois formula [17]: 0.0001 x 71.84 x (weight in kg)^0.425 x (height in cm)^0.725. Three measurements were made and averaged. Left ventricular hypertrophy was defined as a value of LVMi ≥ 110 g/m² for men and ≥ 106 g/m² for women [18]. Relative wall thickness was calculated according to the following ratio: 2 PWTd/LVIDd. Concentric LHV was defined as a relative wall thickness ≥ 0.45, while eccentric LVH was < 0.45 [19].

Pulsed Doppler examinations of left ventricular inflow were performed with the 2.5 MHz transducer. Using the apical four-chamber view, the Doppler sample volume was placed in the mitral valve tunnel just on the left ventricle of the mitral annulus, and its position along the cursor line was adjusted until the highest peaks of diastolic flow velocity were recorded and the graphic quality of the Doppler waveform was optimal [20]. Mitral flow signals included early (E) and late peak velocity (A).

Twelve of the 92 participants were excluded because of inability to obtain an adequate echocardiographic tracing of the left ventricle and/or asymmetrical septal hypertrophy (IVSTd/PWTd > 1.3). Table I shows the clinical characteristics of the 80 patients who were further considered in this study.

Other cardiologic investigations – The entire study group underwent a bicycle ergometer stress test, dipyridamole thallium myocardial scintigraphy and 48-h ambulatory ECG monitoring, as previously described [10]. The investigators from the two centres
Bondy and Reims) had agreed on common positive criteria for myocardial ischaemia.

Briefly, the ECG stress test consisted of a graded exercise test on a bicycle ergometer, starting from a workload of 30 W and increasing by 30 W every 3 min. The test was considered to be positive if either angina pectoris occurred or there was an ST-segment horizontal or downsloping depression ≥ 0.1 mV at 0.08 sec beyond the J point, or ventricular ectopic activity (more than 5 ventricular premature contractions per min, or complex ventricular premature contractions: couplets, ventricle tachycardia, or multiform), or atrioventricular blockade or intraventricular bundle blockade. Occurrence of angina pectoris was considered to be a criterion for exclusion from the study. The ECG stress test was monitored by the same investigator in each centre, and all ECG recordings were read by both investigators independently and blindly.

Thallium-201 myocardial scintigraphy was performed using pharmacologic stress testing, which consisted of infusing 0.56 mg/kg dipyridamole intravenously for 4 min. Three or 4 mCi of thallium-201 were administered 4 min after completion of dipyridamole infusion when body weight was under 75 kg or above 90 kg respectively. Myocardial scintigraphy was performed by a single investigator in each centre, and all images were read by both investigators independently and blindly. The test was considered to be positive when transient defects were observed by both investigators. Defects strictly localised to the apex or base were not considered significant.

Ambulatory electrocardiographic monitoring was performed with an Avionics device during hospitalisation. Two channel recordings (leads V5 and V5R) were obtained. The test was considered positive if either a horizontal ST-segment depression ≥ 1.5 mm lasting ≥ 1 min or a horizontal or convex ST-segment elevation ≥ 1.5 mm lasting ≥ 1 min occurred 0.08 s beyond the J point for a heart rate < 100 beats/min or 0.08 s after the J point for a heart rate > 100 beats/min (taking the isoelectric line of three consecutive PR segments as the reference line). All recordings were analysed by the same investigator.

If ischaemic heart disease was suggested by one or more of these non-invasive tests, coronary angiography was performed. Coronary stenosis was considered significant when ≥ 50 % narrowing was found on the left coronary artery, or ≥ 70 % narrowing on the left anterior descending artery or circumflex or on a well-developed marginal vessel or the right coronary artery.

Table I. Clinical characteristics, silent myocardial ischemia and cardiac autonomic neuropathy.

<table>
<thead>
<tr>
<th></th>
<th>Whole study group</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>80</td>
<td>14</td>
<td>66</td>
</tr>
<tr>
<td>Males/females</td>
<td>47/33</td>
<td>13/1</td>
<td>34/32</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>53.9 ± 9.4</td>
<td>48.6 ± 11.3</td>
<td>55.1 ± 8.7</td>
</tr>
<tr>
<td>Duration of diabetes (yrs)</td>
<td>16.4 ± 8.5</td>
<td>24.7 ± 9.7</td>
<td>14.7 ± 7.0</td>
</tr>
<tr>
<td>Smokers</td>
<td>38</td>
<td>10</td>
<td>28</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>34</td>
<td>10</td>
<td>24</td>
</tr>
<tr>
<td>Hypertension</td>
<td>58</td>
<td>10</td>
<td>48</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>12</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.9 ± 5.3</td>
<td>23.6 ± 2.7</td>
<td>28.8 ± 5.3</td>
</tr>
<tr>
<td>Waist/hip circumferences</td>
<td>1.02 ± 0.07</td>
<td>1.05 ± 0.04</td>
<td>1.01 ± 0.07</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>144 ± 15</td>
<td>143 ± 17</td>
<td>144 ± 15</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>85 ± 9</td>
<td>86 ± 11</td>
<td>85 ± 9</td>
</tr>
<tr>
<td>Silent myocardial ischemia</td>
<td>26</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>Coronary stenoses</td>
<td>7</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Cardiac autonomic neuropathy</td>
<td>28a</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>Antihypertensive treatment</td>
<td>40</td>
<td>6</td>
<td>34</td>
</tr>
</tbody>
</table>

a Assessed in 66 patients
Cardiac autonomic neuropathy was looked for by standardised tests (lying to standing, deep breathing, Valsalva’s manoeuvre) based on the study of heart rate variations, as previously described [21]. Tests were performed with a microcomputer-based system (AUTOCAFT) on a BBC Master system (ACORN Computers Ltd, Cambridge, UK) [22]. Since the results of cardiac autonomic function tests are influenced by age [23], the results were compared with a previously published series of healthy controls, as previously shown [24]. Because of the possible confounding effect of drugs or the impossibility of performing Valsalva’s manoeuvre due to severe retinopathy, the data concerning these tests were reliably completed in only 66 patients. Cardiac neuropathy was considered to be present when at least one test was abnormal, with age being taken into account.

**Biological measurements** – Serum total cholesterol, HDL-cholesterol, apoproteins A1 and B, and triglycerides were assayed. LDL-cholesterol was calculated according to the Fried-
wald formula. The urinary albumin excretion rate was measured by laser immunonephelometry on one 24-h urine collection, and data was log-transformed to obtain a Gaussian distribution. Creatininemia, fasting and postprandial blood glucose, and HbA1c (on column chromatography) were also assayed. The deformability of red blood cells (RBC) was studied in 40 patients investigated at one of the centres (Jean Verdier Hospital) by measuring their filterability with the Hanss haemorheometer, as previously described [11]. Briefly, RBC suspensions were prepared, and the initial filtration rate was determined by measuring the time taken by RBC to cross through a 13 mm diameter calibrated porous membrane (Nucleopore filter) with a pore diameter of 5 µm. The filtration index was defined by the \([Ts – Tb)/Tb\) \times 100/H ratio, where Ts and Tb are the filtration times of the RBC suspension and the Hank buffer respectively, and H the haematocrit. The higher the filtration index is, the less deformable RBC are.

## STATISTICAL ANALYSES

Results are expressed as the mean ± SD. Comparisons of quantitative parameters in various groups were performed by ANOVA or the Mann and Whitney test according to the Gaussian or non-Gaussian distribution of values. Linear correlations between LVMI and quantitative parameters were calculated. Patients with or without LVH were compared according to different qualitative parameters using chi-square tests. When univariate analysis showed a significant correlation between LVMI and several parameters, multivariate analysis was performed according to multiple linear regression analysis.

### RESULTS

**Echocardiographic results in the entire series** – An adequate echocardiographic tracing was available for 80 patients (47 men, 33 women). LVH was present in 36 patients and considered to be eccentric in 70.6% and concentric in 29.4% of cases.

*Table II* compares the clinical and biological characteristics of the patients with and without LVH. The prevalence of LVH was slightly higher in men (53.2%) than in women (33.3%) (p = 0.08) and not significantly different in Type 1 (28.6%) and Type 2 (48.5%) diabetic patients. Patients with LVH were significantly older (p = 0.031), more often hypertensive (p = 0.010) with a higher systolic blood pressure (p = 0.003), and had a significantly higher value for the waist/hip girth ratio (p = 0.012). There was no significant difference in the prevalence of LVH according to smoking habits, presence or absence of peripheral arterial disease, retinopathy, diabetic nephropathy, or cardiac autonomic neuropathy. The metabolic parameters and the RBC filtration index did not differ significantly in patients with LVH as compared to those without. Creatininemia was significantly higher in patients with LVH (p = 0.025) (*Table II*).

Multivariate analysis was carried out, taking LVMI as a dependent variable and age, the waist/hip girth ratio, systolic blood pressure and creatininemia as independent variables. A significant correlation was found only between LVMI and age and creatininemia: multiple correlation coefficient = 0.419, F = 6.398 (p = 0.003).

*Table III* compares echographic parameters in patients with and without LVH. In patients with LVH, IVSTD, PWTd and LVId were significantly higher

<table>
<thead>
<tr>
<th></th>
<th>LVH</th>
<th>No LVH</th>
<th>p value</th>
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<tbody>
<tr>
<td>n</td>
<td>36</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>IVSTD (mm)</td>
<td>11.4 ± 1.8</td>
<td>9.5 ± 2.0</td>
<td>0.0001</td>
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<tr>
<td>PWTd (mm)</td>
<td>9.9 ± 1.6</td>
<td>8.2 ± 1.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>LVId (mm)</td>
<td>51.1 ± 4.6</td>
<td>45.5 ± 5.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>133.0 ± 24.0</td>
<td>83.0 ± 17.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.39 ± 0.07</td>
<td>0.37 ± 0.10</td>
<td>0.310</td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>36.0 ± 8.5</td>
<td>30.8 ± 5.7</td>
<td>0.002</td>
</tr>
<tr>
<td>E Doppler wave (m/sec)</td>
<td>0.61 ± 0.13</td>
<td>0.60 ± 0.13</td>
<td>0.827</td>
</tr>
<tr>
<td>A Doppler wave (m/sec)</td>
<td>0.73 ± 0.20</td>
<td>0.67 ± 0.17</td>
<td>0.186</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.85 ± 0.23</td>
<td>0.96 ± 0.27</td>
<td>0.038</td>
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</tbody>
</table>

Left atrial diameter was also significantly greater, whereas the E/A velocity ratio was significantly lower in patients with LVH.

Silent myocardial ischaemia – The three noninvasive tests were normal in 54 patients. The other 26 patients were considered to have signs of silent myocardial ischaemia as at least one of these tests was positive. The exercise stress test was positive in 17 cases, myocardial scintigraphy in 10 cases and 48-h ECG monitoring in 5 cases. Four of these patients had Type 1 diabetes and the other 22 had Type 2 diabetes. Coronary angiography was performed in 21 of the 26 patients with signs of SMI, but was refused by the other 5. Significant coronary stenoses were found in 7 patients (4 on the left coronary artery, 1 on the right coronary artery and 2 on both the left and right coronary arteries), whereas the coronary arteries were angiographically normal in the other 14 patients.

Correlates of left ventricular mass according to the presence or absence of silent myocardial ischaemia and coronary stenoses – A correlation was looked for between LVMI and age, the waist/hip girth ratio, systolic blood pressure, creatininaemia, the log urinary albumin excretion rate, cardiac autonomic neuropathy and the RBC filtration index. In the 7 patients with significant coronary stenoses, LVMI was significantly higher (130.0 ± 24.7 g/m²) than in those with SMI and no coronary lesions (102.7 ± 33.4 g/m²) or those without SMI (102.4 ± 32.8 g/m²) (p < 0.05), and correlated significantly with systolic blood pressure (r = 0.923, p = 0.0003). Six of these 7 patients had LVH.

In patients with no sign of SMI – LVMI correlated significantly with systolic blood pressure and creatininaemia (Table IV). LVMI did not differ significantly in patients with nephropathy (albuminuria > 30 mg/24 h; n = 13) and those without nephropathy (albuminuria < 30 mg/24 h) (n = 29) (103.2 ± 48.4 g/m² vs 103.2 ± 29.6 g/m²), nor was there a significant difference between patients with (n = 21) and without (n = 24) cardiac autonomic neuropathy (109.4 ± 39.1 g/m² vs 94.8 ± 25.9 g/m² respectively). In the subgroup of normotensive patients, LVMI was also very similar in those with (n = 7) or without (n = 8) cardiac autonomic neuropathy (89.8 ± 19.1 g/m² vs 95.1 ± 13.3 g/m² respectively). In multivariate analysis, performed with systolic blood pressure and creatininaemia as independent variables in the entire group of patients free of SMI, LVMI correlated only with creatininaemia (r = 0.269, F = 4.072, p = 0.049).

In patients with signs of SMI: but normal coronary arteries on angiography, LVMI correlated significantly with the waist/hip girth ratio, creatininaemia, the log urinary albumin excretion rate, and the RBC filtration index (Table IV, Fig. 1). In multivariate analysis, LVMI correlated with all these parameters, except creatininaemia (multiple correlation coefficient = 0.999, F = 705.73, p = 0.001).

DISCUSSION

Patients with electrocardiographic [1] and echocardiographic [2] LVH have been found to be at high risk for subsequent cardiovascular morbidity and mortality.

In the present study, the diagnostic criteria for LVH were ≥ 110 g/m² for men and ≥ 106 g/m² for women, values representative of the sex-specific 95th percentile of a previously published reference standard in a normal population [18] based on Penn Convention.

<table>
<thead>
<tr>
<th></th>
<th>SMI-</th>
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<th>SMI+ but normal coronary arteries</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>r</td>
<td>p</td>
<td>n</td>
<td>r</td>
</tr>
<tr>
<td>Age</td>
<td>54</td>
<td>0.213</td>
<td>0.122</td>
<td>14</td>
<td>0.393</td>
</tr>
<tr>
<td>Waist/hip circumferences</td>
<td>54</td>
<td>0.148</td>
<td>0.400</td>
<td>14</td>
<td>0.719</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>54</td>
<td>0.288</td>
<td>0.036</td>
<td>14</td>
<td>0.240</td>
</tr>
<tr>
<td>Creatininemia</td>
<td>54</td>
<td>0.269</td>
<td>0.049</td>
<td>14</td>
<td>0.728</td>
</tr>
<tr>
<td>Log urinary albumin excretion rate</td>
<td>42</td>
<td>0.064</td>
<td>0.686</td>
<td>14</td>
<td>0.791</td>
</tr>
<tr>
<td>Filtration index of erythrocytes</td>
<td>26</td>
<td>-0.095</td>
<td>0.644</td>
<td>8</td>
<td>0.955</td>
</tr>
</tbody>
</table>
measurements. The echocardiographic measurement of LVM revealed LVH in 36/80 (45%) of participants, despite the virtual absence of ECG criteria for LVH (data not shown). It is noteworthy that half of the participants had previously undergone antihypertensive therapy, which may have reduced LVM. Seventy point six percent had eccentric and 29.4% concentric LVH. These percentages are similar to results in studies of a mild to moderately hypertensive population [19].

Few studies have compared LV structure in diabetic patients with a control group. In an earlier study [3] (two-dimensional cursor control was lacking at that time), 49 diabetic patients without ischaemic heart disease (26 Type 1, 23 Type 2) were compared to 32 controls. IVSTd was found to be hypertrophied in diabetic patients with retinopathy, and PWTd to be hypertrophied in Type 2 patients. A study with M-mode echocardiography performed on 104 young Type 1 diabetic patients (2 to 24 years old) revealed an interventricular septum hypertrophy in some patients over 12 years of age [4].

Previous studies in adults with diabetes demonstrated abnormalities in diastolic filling, including a decreased peak filling rate and a greater dependence on atrial contraction for ventricular filling [25-27]. In the present study, the pattern of ventricular filling, characterised by a lower E/A ratio (early/late peak velocity) and a greater left atrial diameter in patients with LVH than in those without, may have resulted from abnormal ventricular relaxation or decreased ventricular compliance. This strongly suggests the involvement of LVH in filling abnormalities.

The determinants of LVH in diabetic patients are not well-known. The influence of hypertension is not the only possibility, and the association of LVH with nephropathy and cardiac autonomic neuropathy has been suggested [5-7]. However, SMI is a frequent complication of diabetes [8-10] and may be associated with a change in LVMI. Thus, the main purpose of the present study was to examine the determinants of LVH in diabetic patients according to the presence or absence of SMI.

The influence of hypertension on LVH was strongly suggested in the group of 7 patients with significant coronary stenoses because of the highly significant correlation found between LVMI and systolic blood pressure. In the entire series, LVH was also associated with a higher prevalence of hypertension. Nevertheless, this association was not significant in multivariate analysis. These results do not exclude the role of hypertension in the development of LVH since 69% (40 out of 58) of hypertensive patients were treated by one or several drugs, though they are consistent with the influence of other factors besides hypertension. Two other studies [5, 28] have also suggested that diabetes mellitus accelerates the development of LVH independently of blood pressure.

Sampson et al. [29] have shown that mean interventricular septal width was significantly increased in diabetic patients with microalbuminuria and proteinuria, and that the greatest width was noted in diabetic patients with renal impairment. The relationship between LVH and nephropathy was also suggested by Grenfell et al. [6] who found LVH in 42 of 49 patients with overt diabetic nephropathy (85%). LVH was present even in patients with slightly elevated blood pressure.

![Fig. 1. Correlation between the left ventricular mass index (LVMI) and the filtration index of red blood cells in diabetic patients with silent myocardial ischemia but normal coronary arteries on angiography (r = 0.955, p = 0.0001).](image-url)
pressure and was related to age and serum creatininemia but not to blood pressure or duration of proteinuria. For our entire study group, multiple regression analysis showed a relationship between LVMI and age and creatininemia independently of other potential determinants such as systolic blood pressure and the waist/hip girth ratio. Moreover, the correlation between LVMI and renal function was again found in patients strictly free of SMI, independently of blood pressure.

In the subgroup of patients with signs of SMI and no coronary stenosis, LVMI correlated strongly with three factors: the waist/hip girth ratio, the RBC filtration index and albuminuria. The waist/hip girth ratio has been shown to be an independent risk factor for cardiovascular disease and death [30-32]. Obesity has also been found to be associated with increased left ventricular wall thickness and left ventricular mass in both hypertensive and normotensive subjects [33, 34]. Our results suggest that abdominal adiposity may be associated with poor cardiovascular prognosis in diabetic patients via an increase in LVMI. Concerning the second factor, an increase in whole blood viscosity has been found to be a determinant of LVH in hypertensive patients [13]. The increase in the RBC filtration index, an indicator of poor RBC deformability, has been clearly demonstrated in diabetic patients [11, 12]. The present results strongly suggest that this disorder, as in hypertensive patients, may be a determinant of left ventricular mass in diabetic patients with signs of SMI but with angiographically normal coronary arteries. It may deteriorate the microcirculatory conditions in the myocardium and contribute to the positive results of the stress test and myocardial scintigraphy in these patients by reducing myocardial oxygen delivery. A reduction in coronary vascular reserve and acetylcholine-induced coronary vasodilation has been found in some of these patients [35, 36], which may be another explanation for the positive non-invasive tests. With respect to the third factor, nephropathy could reflect generalised vasculopathy secondary to endothelium dysfunction [37]. Increased cardiovascular mortality in patients with albuminuria is only partly due to a higher prevalence of cardiovascular risk factors. Thus, microalbuminuria is not only an indicator for renal disease but also a strong and independent risk factor for cardiovascular death [38-40]. The present data suggest that the poor prognosis associated with nephropathy may be related to an increase in left ventricular mass.

Gambardella et al. [7] studied the possible relationship between cardiac autonomic neuropathy and LVMI in 27 normotensive diabetic patients. Increased LVMI, septal wall thickness, and posterior wall width were observed in neuropathic patients who showed very few changes from day to night in systolic, diastolic and mean blood pressure. Increased LVMI was ascribed to nocturnal blood pressure. However, we failed to find any correlation between LVMI and cardiac autonomic neuropathy in our series of asymptomatic diabetic patients. In particular, there was no correlation in the group of normotensive diabetic patients free of SMI. These discrepancies might have resulted from patient selection since some patients investigated by Gambardella et al. [7] might have had undetected SMI or even coronary stenoses which might have changed the LVMI.

■ CONCLUSION

The results of this study indicate that diabetes was associated with LVH in nearly half of patients with two additional risk factors, and that LVH was responsible for early LV filling abnormalities and may have been an early marker of diabetic cardiomyopathy. The main determinants of the increase of LVMI seem to differ according to the presence or absence of SMI and coronary stenoses. Blood pressure seems to play a major role in LVH, in association with coronary stenoses. The correlation between LVMI and renal function previously reported in diabetic patients was found here only in patients free of SMI. Together with the excentric nature of LVH in most cases, this correlation suggests the influence of volume load. The most interesting result concerns the group of patients with SMI according to non-invasive tests but who had angiographically normal coronary arteries. The strong correlation between LVMI and albuminuria and increased red blood cell rigidity in this group is consistent with the involvement of microcirculatory disorders in the increase of LVMI and the positivity of these tests. Finally, these findings, which need to be confirmed in a larger sample of patients, suggest that different therapeutic approaches should be considered in the prevention or limitation of LVH in diabetic patients.

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