Left ventricular mass in hypertensive patients with mild-to-moderate reduction of renal function

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SUMMARY AT A GLANCE

A high prevalence of Left ventricular hypertrophy exists in patients with mild or moderate renal dysfunction.

ABSTRACT:

Aim: Left ventricular hypertrophy (LVH) is an independent predictor of cardiovascular (CV) morbidity and mortality. The aim of the present study was to evaluate the relationship between LV mass and mild-to-moderate renal dysfunction in a group of non-diabetic hypertensives, free of CV diseases, participating in the Renal Dysfunction in Hypertension (REDHY) study.

Methods: Patients with diabetes, a body mass index (BMI) of more than 35 kg/m², secondary hypertension, CV diseases and a glomerular filtration rate (GFR) of less than 30 mL/min per 1.73 m² were excluded. The final sample included 455 patients, who underwent echocardiographic examination and ambulatory blood pressure monitoring.

Results: There was a significant trend for a stepwise increase in LV mass, indexed by both body surface area (LVMI) and height elevated to 2.7 (LVMH².⁷), with the declining renal function, that remained statistically significant after correction for potential confounders. The prevalence of LVH, defined either as LVMI of 125 g/m² or more or as LVMH².⁷ of 51 g/m².⁷ or more, was higher in subjects with lower values of GFR than in those with normal renal function (P < 0.001 in both cases). The multiple regression analysis confirmed that the inverse association between GFR and LVM was independent of confounding factors.

Conclusion: The present study confirms the high prevalence of LVH in patients with mild or moderate renal dysfunction. In the patients studied (all with a GFR of 30 mL/min per 1.73 m²), the association between LVM and GFR was independent of potential confounders, including 24 h blood pressure load. Taking into account the negative prognostic impact of LVH, further studies focusing on a deeper comprehension of the mechanisms underlying the development of LVH in chronic kidney disease patients are needed.
While for patients with ESRD data regarding the prevalence and the prognostic significance of LVH are well-consolidated, less data are available about the relationship between LVH and less advanced CKD. However, published data seem to provide evidence that the prevalence of LVH among non-uremic CKD patients is 34–78%, with increasing prevalence along with decreasing renal function.9

The aim of our study was to evaluate the relationship between LV mass and mild-to-moderate reduction of kidney function in a group of non-diabetic hypertensive patients, free of CV diseases, participating in the Renal Dysfunction in Hypertension (REDHY) study.10

METHODS

The study was conducted in accordance with the Declaration of Helsinki and the enrolled patients agreed to participate after informed consent.

Study population

Patients were recruited among the subjects participating in the REDHY study,10 consecutively attending our hypertension centre, in which good quality echocardiographic examination and ambulatory blood pressure monitoring (ABPM) were available. Among 556 patients who underwent both the exams, 31 were excluded due to bad quality ABPM, and 60 due to bad quality echocardiogram.

Study subjects underwent a detailed review of their medical history, clinical examination and exams to exclude secondary forms of hypertension.

Exclusion criteria were: diabetes of fasting glycemia of 7 mmol/L or more; a body mass index (BMI) of more than 35 kg/m²; history of nephroparenchymal, renovascular, endocrine or malignant hypertension; proteinuria and hematuria; history of glomerulonephritis or nephroparenchymal, renovascular, endocrine or malignant hypertension (MDRD) study equation: 13 186

\[
\text{GFR} = \frac{186 \times \text{serum creatinine (mg/dL)}^{\frac{2}{3}} \times \text{age (years)}^{0.203} \times 0.742}{\text{weight (kg)}}
\]

The ethnicity factor \(0.803\) if black) of the equation was not used because all the subjects enrolled in our study were white. This method was used for the selection and classification of patients. In the enrolled subjects, GFR was also estimated by the Cockroft-Gault formula,14 creatinine clearance rate,15 both corrected by body surface area, and by the quadratic equation of the Mayo Clinic.13 We chose to analyze data using four different equations for estimating GFR due to lack of good validity of the different equations in people with near-normal creatinine. Using these four equations allowed us to control our results, thus minimizing a possible bias derived from the method chosen to estimate GFR.

Patients were divided into three groups according to the levels of renal function, using the cut-off values of GFR proposed by the National Kidney Foundation Kidney Disease Outcome Quality Initiative (K/DOQI):16 group 1 (normal kidney function), GFR of 90 mL/min per 1.73 m² or more; group 2 (mild reduction of GFR), GFR of 60–89 mL/min per 1.73 m²; and group 3 (moderate reduction of GFR), GFR 30–59 mL/min per 1.73 m².

Laboratory methods

Serum and urine creatinine concentrations were determined by the kinetic picrate method using an auto-analyser (Monarch 2000 auto-analyser, Instrumentation Laboratories, Lexington, MA, USA).

The same analyser was used to determine the other routine biochemical parameters.

Twenty-four hour urine albumin excretion (AER) was determined by the radioimmunoassay method (Techno Genetics RIA Kit, Milan, Italy). Albuminuria was defined as AER of more than 20 µg/min.

ABPM

A portable, non-invasive SpaceLabs 90207 recorder (Redmond, Washington, USA) performed the 24 h ABPM. BP readings were performed automatically at 15 min intervals during the day (07.00–22.00 hours) and at 20 min intervals during night-time resting (22.00–07.00 hours). The reading, editing and analysis of the data provided by the recorders were carried out by the SpaceLabs ABP90209 interface ver. 2.40.23. Systolic readings greater than 260 mmHg or less than 70 mmHg, diastolic readings higher than 150 mmHg or less than 40 mmHg, and pulse pressure readings above 150 mmHg or below 20 mmHg were automatically discarded.

Only records with more than 80% of valid data were accepted.

Echocardiography

Echocardiography was performed using an Acuson Sequoia 512 system (Siemens, Mountain View, CA, USA). M-mode echocardiography was performed according to the American Society of Echocardiography (ASE) recommendations.17 Images were taken in a partial left lateral decubitus position performed to evaluate left ventricular end-diastolic and end-systolic diameter, interventricular septum thickness and posterior wall thickness.

Only those frames with optimal visualization of interfaces and showing simultaneous visualization of the septum, left ventricular diameters and posterior wall were used for readings.

Left ventricular mass (LVM) was determined using the formula proposed by Devereux et al.18 and was indexed by both body surface area (LVMi) and height elevated to a power of 2.7 (LVMH²).19

Left ventricular hypertrophy was defined as LVMi of 125 g/m² or more or LVMH² of 51 g/m² or more.19

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Echocardiographic data are expressed as the average of five consecutive cardiac cycles. Images were read by a single cardiologist, who was blinded to the patient’s clinical characteristics.

**Statistics**

Data for continuous variables are given as mean ± standard deviation.

Albumin excretion had a skewed distribution, and was expressed as median and interquartile range. It was log-transformed to achieve normal distribution before use in parametric statistical tests. LVMI and LVMH^{2.7} also showed a skewed distribution. However, because the application of nonparametric tests to these variables or their mathematical transformations (log transformation) provided similar results to those obtained using parametric tests or untransformed data, we have used only the latter in our paper, even if they were points to those obtained using parametric tests or untransformed data.

Differences between groups were evaluated using ANOVA and Student’s t-test, with Bonferroni corrections, for continuous variables, and the χ²-test, with Yates’ correction, for the categorical variables.

For the comparisons regarding LV mass between the groups with different levels of renal function, we used also the Kruskal–Wallis test.

When appropriate, differences were adjusted, by ANCOVA, for age, 24 h systolic and diastolic BP and uricemia.

Associations between variables were tested using Pearson’s coefficients (r), Spearman’s correlation analysis (p) and multiple stepwise regression analyses. The latter was performed considering LVMI (or LVMH^{2.7}) as the dependent variable and included in the statistical models those variables associated with LVM in univariate analyses (age, sex, BMI, known duration of hypertension, previous antihypertensive treatment, 24 h systolic and diastolic BP, AER, GFR, uricemia) and smoking status.

Multiple regression analysis was repeated replacing BMI with waist circumference, 24 h systolic BP with clinical systolic BP, or estimating GFR by means of Cockcroft–Gault equation, creatinine clearance or Mayo Clinic equation.

The null hypothesis was rejected at two-tailed P < 0.05.

The statistical analyses were performed using the Systat Data software package ver. 11 (Systat, Richmond, CA, USA).

**RESULTS**

The principal demographic and clinical characteristics of studied patients are synthesized in Table 1.

Table 2 shows some clinical characteristics of patients stratified according to their level of renal function. The comparison between groups showed that patients with lower estimated GFR were older, had higher BP (both clinical and 24 h readings), had higher uricemia and were more frequently treated when compared with patients with normal renal function. The three groups did not differ significantly with regard to glycemia, triglycerides, high-density lipoprotein cholesterol, total cholesterol, smoking status, BMI, waist circumference, AER and known duration of hypertension.

Left ventricular mass, indexed by both body surface area (LVMI) (Fig. 1) and by height elevated to a power of 2.7 (LVMH^{2.7}) (Fig. 2), was progressively higher comparing
subjects with different degrees of renal function, even after correction (ANCOVA) for potential confounders such as age, 24 h systolic and diastolic BP, and uricemia ($P < 0.001$).

In the overall population, the prevalence of LVH, defined as LVMI of 51 g/m$^2$ or more, was 41.5%. When we analyzed globally subjects with mild-to-moderate reduction in renal function ($n = 244$), LVH prevalence was 33.2% considering LVMI and 50% considering LVMH$^{2.7}$. Moreover, LVH prevalence increased along with lessening renal function ($\chi^2$: $P < 0.001$ in both cases, Fig. 3). Indeed, with regard to patients with GFR of 59–30 mL/min per 1.73 m$^2$, the prevalence of LVH was very high: 48.6% considering LVMI and 65.7% considering LVMH$^{2.7}$ (Fig. 3).

Table 3 displays the univariate correlations obtained between GFR, estimated with different methods, and LVMI. Figure 4 shows the relationships between LVMI, LVMH$^{2.7}$ and GFR estimated by the MDRD equation.

The independent association between GFR and LVM was confirmed by the multiple stepwise linear regression analysis, conducted considering LVMI (or LVMH$^{2.7}$) as dependent variable and including in the statistical models age, sex, BMI, known duration of hypertension, previous anti-hypertensive treatment, 24 h systolic and diastolic BP, AER, GFR, uricemia and smoking status.

Glomerular filtration rate estimated by the MDRD equation (Table 4), along with age ($\beta = 0.15$; $P < 0.05$), sex ($\beta = 0.22$; $P < 0.005$), 24 h systolic BP ($\beta = 0.20$; $P < 0.005$) and AER ($\beta = 0.13$; $P < 0.05$), were independently associated with LVMI. The proportion of variability in LVMI that was explained by this model was 26% ($R^2 = 0.26$). The estimated increase in LVMI for every mL/min decrease in GFR was 0.24 g/m$^2$ (95% confidence intervals, 0.41–0.07).

The independent predictors of LVMH$^{2.7}$, in a model that accounted for 28% of its total variance, were GFR (Table 4), age ($\beta = 0.16$; $P < 0.05$), BMI ($\beta = 0.23$; $P < 0.005$), 24 h systolic BP ($\beta = 0.22$; $P < 0.005$) and AER ($\beta = 0.12$; $P < 0.05$). The inclusion into the statistical model of waist circumference instead of BMI, or of clinic systolic and diastolic BP instead of 24 h systolic and diastolic BP, did not modify the results. The same was true when GFR was estimated by the Cockcroft–Gault formula, the creatinine clearance, or the Mayo Clinic equation, instead of the MDRD equation (Table 4). When we run again multiple regression models replacing 24 h systolic BP with 24 h pulse pressures, the standard regression coefficients relating GFR with LVM did not materially change.

**DISCUSSION**

The main findings of our study, which involved 455 non-diabetic hypertensive subjects without CV complications and with mild-to-moderate reduction of kidney function, are: (i) the progressive increase of LV mass and of LVH prevalence along with decreasing renal function; and (ii) the inverse association between GFR and LVM, independently by potential confounders such as, in particular, 24 h BP load, which was significantly increased in subjects with more advanced renal dysfunction (Table 2).

It is well-known that LVH, frequent expression of subclinical target-organ damage related to hypertension, is independently associated with CV risk. Structural and functional LV anomalies in CKD patients were frequently reported in the published work. However, available data are mainly

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**Table 1** Principal demographic and clinical characteristics of 455 hypertensive patients

| Age (years) | 48.3 ± 14.4 |
| Sex (M/F) (%) | 54/46 |
| Smoking status (yes/no) (%) | 31/69 |
| Clinic SBP/DBP (mmHg) | 154/92 ± 21/16 |
| 24-h SBP/DBP (mmHg) | 134/83 ± 14/12 |
| Known duration of hypertension (years) | 7 ± 7.5 |
| Previous antihypertensive treatment (yes/no) (%) | 76/24 |
| Body mass index (kg/m$^2$) | 28.7 ± 4.8 |
| Waist circumference (cm) | 96.5 ± 13.3 |
| Glycemia (mmol/L) | 5.035 ± 0.06 |
| Triglycerides (mmol/L) | 1.61 ± 0.86 |
| HDL cholesterol (mmol/L) | 1.18 ± 0.27 |
| Total cholesterol (mmol/L) | 5.3 ± 1.06 |
| Uricemia (µmol/L) | 291 ± 89 |
| AER (µg/min) | 8.4 (5–18.3) |
| GFR (mL/min/1.73 m$^2$) | 90 ± 24 |

AER, albumin excretion rate; GFR, glomerular filtration rate; HDL, high-density lipoprotein; SBP/DBP, systolic/diastolic blood pressure.

**Table 2** Some clinical characteristics of the study subjects, stratified according to the levels of renal function

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Uricemia (mmol/L)</th>
<th>Subjects previously treated with antihypertensive drugs (%)</th>
<th>Clinic SBP/DBP (mmHg)</th>
<th>24 h SBP/DBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 ($n = 211$)</td>
<td>42.4 ± 13.9</td>
<td>274 ± 77.3</td>
<td>68</td>
<td>153/91 ± 21/15</td>
</tr>
<tr>
<td>Group 2 ($n = 209$)</td>
<td>52.7 ± 12.4</td>
<td>303 ± 89.2</td>
<td>83</td>
<td>154/92 ± 20/15</td>
</tr>
<tr>
<td>Group 3 ($n = 35$)</td>
<td>57.6 ± 13.6</td>
<td>381 ± 89.2</td>
<td>86</td>
<td>173/102 ± 21/16</td>
</tr>
<tr>
<td>$P$</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001/0.0001 = 0.003/0.0001</td>
</tr>
</tbody>
</table>

Group 1, GFR 90 mL/min per 1.73 m$^2$; group 2, GFR 89–60 mL/min per 1.73 m$^2$; group 3, GFR 59–30 mL/min per 1.73 m$^2$. GFR, glomerular filtration rate; SBP/DBP, systolic/diastolic blood pressures.
referred to patients with advanced renal dysfunction. Among patients with ESRD starting renal replacement therapy, nearly 15% have systolic dysfunction, nearly 40% have heart failure and more than 70% have LVH.7,9

Although the pathogenesis of LVH in CKD is considered to be multifactorial, hypertension, alterations of hydro-mineral imbalance and anaemia are identified as the major determinants of LV growth. However, other factors, such as an inappropriate activation of the renin–angiotensin–aldosterone system, oxidative stress, inflammation and the hyperactivation of collagen and muscle cells growth factors may have a relevant role.

From a haemodynamic view, LVH is primarily an adaptive remodelling process, compensating for an increase in cardiac work, which may be schematically due to volume and/or pressure overload. Schematically, pressure overload, caused for example by hypertension or aortic stenosis, leads to concentric hypertrophy, while volume overload, caused for example by anaemia, by expansion of hydro-mineral volume or (in patients on haemodialysis) by the presence of an arteriovenous fistula, leads to the development of eccentric hypertrophy.20

Both patterns of LVH are frequent among patients with CKD, and often a mixed pattern, characterized by the increase of both diameters and wall thicknesses, can be recognized.21

While data regarding LVH in ESRD patients are well consolidated, the association between LVH and mild renal dysfunction has been less studied.

In a study by Levin et al.,9 of the 318 CKD patients enrolled, 34% had LVH, whose prevalence increased with the declining renal function, becoming near to 70% in the subgroup with ESRD. After a 1 year follow-up period, systolic BP and the reduction of haemoglobin concentration were the independent predictors of LVM increase. Among the study subjects, 39% had CV diseases at the time of enrolment, and 25.8% had diabetes, while the prevalence of hypertension was not reported. Mean GFR (Cockcroft–Gault equation) was less than 40 mL/min.

Table 3 Univariate correlations (calculated by both the Pearson’s coefficients (r) and the Spearman’s correlation analysis (ρ)) between glomerular filtration rate (GFR) estimated by four different methods and left ventricular mass indexed by body surface area (LVMI) or by height elevated to a power of 2.7 (LVMH2.7)

<table>
<thead>
<tr>
<th></th>
<th>LVMI</th>
<th>LVMH2.7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>ρ</td>
</tr>
<tr>
<td>Estimated GFR (MDRD equation)</td>
<td>−0.26*</td>
<td>−0.25*</td>
</tr>
<tr>
<td>Estimated GFR (Cockcroft–Gault equation)</td>
<td>−0.29*</td>
<td>−0.28*</td>
</tr>
<tr>
<td>Estimated GFR (Mayo Clinic equation)</td>
<td>−0.24*</td>
<td>−0.24*</td>
</tr>
<tr>
<td>Estimated GFR (creatinine clearance)</td>
<td>−0.29*</td>
<td>−0.27*</td>
</tr>
</tbody>
</table>

*P < 0.001. MDRD, Modification of Diet in Renal Disease.
In the Hoorn Study, the association between LVH and renal dysfunction has been evaluated in 742 subjects, nearly 70% of whom were hypertensives. While in women no relation between renal dysfunction and LVM was observed, it was found in men. However, the relation lost statistical significance after the inclusion of some parameters of arterial stiffness in the multivariate analysis.

The authors concluded that renal dysfunction, through an increase of arterial stiffness, leads to the increase of LVM (the authors found an increase of both LV diameter and wall thickness).

Interpreting these data, we should bear in mind some clinical characteristics of the enrolled patients, such as mean GFR (nearly 60 mL/min per 1.73 m² estimated by MDRD).
A study by Paoletti et al. evaluated the prevalence of LVH in 244 non-diabetic patients with CKD, reaching conclusions consistent with those by the Hoorn Study; in fact, an independent association between LVM and pulse pressure was demonstrated. Also in this study, mean age (63 years) was higher than in our study; the prevalence of hypertension was 66%, mean GFR (Cockcroft-Gault equation) was 36 mL/min and, of the 244 patients, 104 (42.6%) had GFR of less than 30 mL/min. Also in this study, the prevalence of LVH was progressively higher along with the declining renal function, being 71% in stage 3 CKD.

Among the limitations of our study, we have to acknowledge the cross-sectional design and the lack of data on arterial stiffness. Although we adjusted for age, demographic characteristics and other variables, we cannot rule out the possibility that unmeasured confounders account for the associations we observed. For example, we did not measure haemoglobin because the data are missing for the majority of patients; however, we believe that this is not an important limitation, because more than 92% of the participants had an estimated GFR of more than 60 mL/min. It is well known that the prevalence of anaemia only noticeably increases at an estimated GFR of less than 60 mL/min per 1.73 m². Therefore, it is likely that in our population the impact of reduced haemoglobin levels on LV mass may be less relevant than in studies in which patients with more severe impairment in renal function were analysed. Moreover, an inverse independent relationship between haemoglobin levels and LV mass has been demonstrated in some, but not all, studies performed in patients with pre-dialysis CKD.

Another possible weakness in our results could be represented by the potential influence on LV mass of previous pharmacological treatment with antihypertensive drugs, even if it was taken into account in the multivariate analyses. Moreover, the percentage of subjects treated with angiotensin-converting enzyme inhibitors or angiotensin II type 1 blockers or other classes of antihypertensive drugs did not differ significantly in the three groups (data not shown).

In conclusion, our study, which evaluated the relationships between LVH and CKD in a group of middle-aged non-diabetic hypertensives without CV diseases, confirms the high prevalence of LVH in patients with mild or moderate renal dysfunction. In the patients studied herein (all with GFR of 30 mL/min per 1.73 m²), the association between LVM and GFR was independent of potential confounders such as age, sex, 24 h BP load and duration of hypertension. Taking into account the high CV risk of CKD patients, and the negative prognostic impact of LVH, further studies focusing on a deeper comprehension of the mechanisms underlying the development of LVH in CKD patients are needed.

Furthermore, there is the need for an early identification of mild or moderate renal dysfunction in hypertensive patients, because it is associated with a higher prevalence of target-organ damage, therefore heightening risk of fatal and non-fatal CV events. The early identification of such patients is needed to carry out an early and aggressive pharmacological treatment.

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REFERENCES


