Mild Renal Dysfunction Is Associated With Electrocardiographic Left Ventricular Hypertrophy


Background: Both renal dysfunction and left ventricular hypertrophy (LVH) are signs of end-organ damage, risk markers of cardiovascular (CV) disease and chronic heart failure. In selected populations such as those with diabetes or hypertension, renal dysfunction was found to be related to LVH. We studied the relation between renal dysfunction and LVH in a cross-sectional study in 8592 inhabitants from Groningen, The Netherlands.

Methods: Standard 12-lead electrocardiograms were recorded, and LVH was classified using the Cornell voltage-duration product. Renal dysfunction was defined as creatinine clearance $< 60 \text{ mL/min/1.73 m}^2$ or microalbuminuria (30 to 300 mg/24 h).

Results: Electrocardiographic signs of LVH were present in 396 of subjects (5.3%). Subjects with LVH were older and had a more extensive CV risk profile. We found that LVH was more prevalent in subjects with renal dysfunction than in those without (8% vs 4%, $P < .001$). Multivariate regression analysis demonstrated that renal dysfunction was independently related to a 1.47-fold increased risk of the presence of LVH (95% CI = 1.15 to 1.88, $P < .009$). In addition, both creatinine clearance (OR = 1.56, 95% CI = 1.07 to 2.2, $P = .044$) and microalbuminuria (OR = 1.37, 95% CI = 1.04 to 1.80, $P = .024$) were independently associated with the presence of LVH.

Conclusion: Subjects with mild renal dysfunction have a substantially higher risk of LVH on electrocardiography than those without renal dysfunction. Am J Hypertens 2005;18:342–347 © 2005 American Journal of Hypertension, Ltd.

Key Words: Left ventricular hypertrophy, renal function, microalbuminuria, PREVEND.

Left ventricular hypertrophy (LVH) is a manifestation of subclinical cardiovascular (CV) end-organ damage and plays a prominent role in CV disease. Several factors in LVH contribute to ventricular dysfunction and chronic heart failure in the long term. The presence of LVH is an important independent risk factor for total and cardiovascular mortality. Impaired renal function is another manifestation of end-organ damage.

Several studies have demonstrated an association between renal dysfunction and LVH. However, these studies were performed only in selected populations, such as in patients with end-stage renal disease, untreated hypertension, or diabetes mellitus type II. Therefore, we investigated the association cross-sectionally between renal dysfunction and electrocardiographic LVH in a large cohort study.

Methods

Study Design and Population

This study was performed in the subjects participating in the Prevention of Renal and Vascular ENd-stage Disease (PREVEND) study. The PREVEND study is designed to investigate prospectively the natural course of albuminuria and its relation to renal and cardiovascular disease in a large cohort drawn from the general population. Details of this study were supported by Dutch Kidney Foundation grant E.013 and by the Netherlands Heart Foundation grant NHS 99.103. Dr. Asselbergs is a research fellow of the Netherlands Heart Foundation (2003T010).

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the study protocol have been described elsewhere. In summary, during the period 1997–1998, all 85,421 inhabitants of the city of Groningen, The Netherlands who were 28 to 75 years of age were sent a one-page postal questionnaire (regarding demographics, use of medication, and pregnancy) and a vial to collect an early morning urine sample. A total of 40,856 subjects responded (47.8%; Fig. 1). Their vials were sent to a central laboratory where urinary albumin and creatinine concentrations were measured. After exclusion of subjects with type 1 diabetes mellitus (defined as use of insulin), women who were possibly pregnant, and men and women not able or willing to participate, all subjects with a urinary albumin excretion (UAE) of ≥10 mg/L (n = 7768, group A) and a random sample of the 22,492 subjects with a UAE <10 mg/L (group B) were invited for further investigations in an outpatient clinic and to collect two consecutive 24-h urines. The random sample was generated by the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL). Taking into regard an expected nonparticipation rate of around 15%, the number of subjects invited to form group B was arbitrarily set at 3395 to achieve an overall sample size of approximately 10,000 subjects. Of group A, 6000 subjects (77.2%) completed the screening protocol and of group B, 2592 subjects (76.3%). These 8592 subjects form the actual PREVEND baseline cohort.

All subjects filled out a questionnaire concerning demographics characteristics and cardiovascular and renal history. Anthropometric and BP measurements were performed.

Fasting blood samples were taken and subjects provided two 24-h urine collections. We excluded 451 subjects because of erythrocyturia or leucocyturia, as these laboratory abnormalities may indicate the presence of urinary tract infection, which makes the assessment of the exact amount of albuminuria unreliable. A total of 117 subjects were excluded because of the presence of macroalbuminuria to rule out overt nephropathy. In addition, 81 subjects were excluded because of missing electrocardiographic data and 17 subject because LVH could not be determined on the electrocardiogram. In all, 7926 subjects were eligible for the analysis.

All subjects gave written informed consent. The local medical ethics committee approved the PREVEND study, which was conducted in accordance with the guidelines of the Declaration of Helsinki.

### Laboratory Methods

Urinary albumin excretion were measured in each collection. Urinary albumin concentrations and high sensitive C-reactive protein were determined by nephelometry (Dade Behring Diagnostics, Marburg, Germany). Leukocytes and erythrocytes were determined by urine stick (Nephur + leuco, Boehringer Mannheim, Germany). Serum glucose, cholesterol, creatinine, and urine creatinine were determined by Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY).

### Definitions

Urinary albumin excretion was measured as the mean of two 24-h urine collections. Normoalbuminuria was defined as urinary albumin excretion of <15 mg/24 h, high normoalbuminuria as urinary albumin excretion of 15 to 29.9 mg/24 h, microalbuminuria as 30 to 300 mg/24 h, and macroalbuminuria as urinary albumin excretion of >300 mg/24 h. Albumin measurements were considered unreliable when >75 leucocytes μL⁻¹ or >50 erythrocytes μL⁻¹ were measured in the urine. Creatinine clearance (CrCl) was calculated as the mean of two 24-h urine creatinine excretions divided by plasma creatinine. Creatinine clearance was adjusted for body surface area, BSA = 0.007184 × weight^{0.425} × length^{0.725}, by dividing CrCl by BSA. Mild renal dysfunction was defined as CrCl <60 mL/min/1.73 m² or the presence of microalbuminuria. To calculate body mass index (BMI), weight (kg) was divided by the square of height (m²). Obesity was defined as BMI >30 kg/m². Diabetes was defined as a fasting plasma glucose level of ≥7.0 mmol/L, a nonfasting plasma glucose level of ≥11.1 mmol/L, or use of oral antidiabetic drugs. Hypertension was defined as systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, or use of antihypertensive medication. Hypercholesterolemia was defined as a serum cholesterol ≥6.5 mmol/L or as serum cholesterol ≥5.0 mmol/L if there was a history of myocardial infarction or use of lipid-lowering medication.
Electrocardiography

Standard 12-lead electrocardiograms were recorded with Cardio Perfect equipment (Cardio Control, Rijswijk, The Netherlands), stored digitally using the computer program Modular Electrocardiogram Analysis System (MEANS, Dr. JA Kors, Rotterdam, The Netherlands). Infarct patterns suggestive of myocardial infarction were defined by Minnesota codes 1.1 and 1.2. Minnesota codes 1.3, 4.1, 4.2, 4.3, 5.1, 5.2, and 5.3 were considered to be indicative for the potential presence for ischemia. The presence of LVH was identified using the Cornell voltage– duration product, which was calculated as follows: RaVL/H(V3) (with 6 mm added in women)/QRS duration. A threshold of 2440 mm · msec was used to identify LVH.11

Statistical Analyses

Differences between continuous variables were tested by the Student t test or Mann-Whitney U test when appropriate. Differences in proportions were tested using a χ² test or Fisher exact test. Continuous variables were modeled with indicator variables into tertiles, and odds ratios (OR) were calculated for the two highest tertiles compared with the lowest (reference) tertile. Logistic regression analysis was performed to determine independent associations with electrocardiographic LVH. Data are expressed as OR and corresponding 95% confidence intervals (CI). Variables with P < .10 in the univariate regression analysis were used in the multivariate regression analysis. A P value < .05 was considered to be significant. Analyses were performed using the statistical software package SPSS 11.0.

Results

Baseline characteristics

Using the Cornell voltage–duration product, 396 subjects (5.3%) were identified with electrocardiographic LVH. Mild renal dysfunction was present in 1311 subjects (16.6% of total population). Creatinine clearance < 60 mL/min/1.73 m² was present in 5.0% and microalbuminuria in 12.9% of the total population. Baseline characteristics of subjects identified with or without LVH are presented in Table 1. Subjects with LVH were significantly older, more frequently male, and had higher BP. Also, diabetes and history of myocardial infarction were more often present in subjects with LVH. Smoking was less common in subjects with LVH (40% vs 45%).

Subjects with mild renal dysfunction had a greater...
frequency of LVH (8% vs 4%; P < .001). Of the subjects with LVH, 186 (47%) did not have hypertension.

**Regression Analysis for LVH**

After adjustment of confounding factors such as age, sex, diabetes, myocardial infarction, systolic and diastolic BP, and use of antihypertensive medication, mild renal dysfunction remained associated with a 1.47-fold (P = .003) increased risk for LVH (Table 2). Because we used a composite parameter renal function, we studied the subjects with microalbuminuria or with a creatinine clearance <60 mL/min/1.73 m² in more detail. In both populations, LVH was equally present. Also, no significant differences were found in age, diabetes, or history of myocardial infarction. Subjects with microalbuminuria tended to be male and to have higher BP. We therefore subdivided the composite parameter renal function (microalbuminuria and creatinine clearance <60 mL/min/1.73 m²), and both remained statistically significant in the multivariate analyses (Table 2). In addition, LVH was significantly associated with systolic BP (respectively for the second and third tertile: OR = 1.24 (95% CI = 0.89 to 1.73) and 1.95 (95% CI = 1.34 to 2.82; P = .001) and a history of myocardial infarction (OR = 2.82, 95% CI = 1.99 to 4.01, P < .001). Figure 2 illustrates the additional value of mild renal dysfunction in subjects with a range of systolic BP.

The association of mild renal dysfunction with LVH was consistent across prespecified subgroups, including men and women, patients with a history of myocardial infarction, those with and without diabetes, those of younger and older age, and those with higher or lower BP (Fig. 3).

Because electrocardiographic LVH has some patterns similar to myocardial ischemia, we adjusted the association of mild renal dysfunction for the presence of ischemia. This did not alter the observed association, indicating that electrocardiographic ischemia was not a confounder (OR = 1.74, 95% CI = 1.36 to 2.21).

In addition, we explored whether the association of mild renal dysfunction and LVH was confounded by the selection criteria of our study population (albuminuria ≥10 mg/L or ≤10 mg/L). The addition of these selection criteria into the multivariate analysis did not alter the association between renal dysfunction and LVH (OR = 1.41, 95% CI = 1.08 to 1.82) and therefore has no effect on the observed association. In a secondary analysis we evaluated interaction terms between the variables of the multivariate analysis and also the selection criteria. No significant interaction term was found in the multivariate analysis.

**Discussion**

This study shows a clear relationship between two manifestations of early cardiovascular end-organ damage, LVH, and renal dysfunction, in an apparently healthy population at large. This association remained statistically significant after adjustment for confounding factors such as age, gender, systolic BP, and myocardial infarction. Interestingly, almost one-half of the subjects with LVH did not have hypertension.

It is important to note that both mild renal dysfunction and LVH are markers of end-organ damage and are known to be well-established risk markers for cardiovascular morbidity and mortality.3,4 The association between mild renal dysfunction and LVH can be explained by several mechanisms. If we assume a causal relationship, a bidirectional interaction is suggested. First, LVH might be caused by renal dysfunction, for example by renal ane-

**Table 2. Multivariate associations with left ventricular hypertrophy**

<table>
<thead>
<tr>
<th>Model</th>
<th>Mild renal dysfunction OR (95% CI)</th>
<th>Microalbuminuria OR (95% CI)</th>
<th>CrCl &lt;60 mL/min/1.73 m² OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>1.97 (1.56–2.48)*</td>
<td>1.95 (1.52–2.50)*</td>
<td>2.01 (1.40–2.88)*</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.73 (1.36–2.19)*</td>
<td>1.70 (1.31–2.20)*</td>
<td>1.72 (1.19–2.49)†</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.47 (1.15–1.88)†</td>
<td>1.37 (1.04–1.80)§</td>
<td>1.56 (1.07–2.29)‡§</td>
</tr>
</tbody>
</table>

Data are expressed as odds ratios (OR) (95% confidence intervals [CI]). Model 1: univariate analysis; Model 2: multivariate model adjusted for age and sex; Model 3: multivariate model final model adjusted for age, sex, diabetes, myocardial infarction, systolic and diastolic blood pressure, and antihypertensive medication.

* P < .001; † P < .01; § both included into the same model.
mia or increased sodium retention, both leading to an increased cardiac workload. Second, renal dysfunction might be caused by LVH, for instance through forward failure by primary conditions such as hypertrophic cardiomyopathy or by secondary conditions such as myocardial infarction or ischemia and aortic valve stenosis. The most probable explanation for the association between LVH and mild renal dysfunction, however, is an intermediate factor that is both associated with renal dysfunction and LVH. These are, for example, hypertension, diabetes, endothelial dysfunction, and activated renin–angiotensin system. Interestingly, angiotensin II type 1 (AT1) antagonists have been proved beneficial in both renal dysfunction and LVH; this may therefore suggest that angiotensin II may play a causal role in the pathophysiology of renal dysfunction, LVH, and their associated increased risk for cardiovascular morbidity and mortality.

The broad definition of renal dysfunction reflects a spectrum of renal conditions that are the result of several pathophysiologic mechanisms in the kidney. Currently it is believed that microalbuminuria, besides being a marker of generalized vascular disease, is a reflection of abnormalities in glomerular filtration rate, for example, glomerular hyperfiltration. Glomerular hyperfiltration is considered as one of the pathophysiologic mechanisms for the development of diabetic and nondiabetic renal disease.

The results of this study may have clinical implications. The increased prevalence of LVH in patients with mild renal dysfunction might explain the increased risk for cardiovascular death. Therefore, physicians should be aware of this association and actively screen for other signs of LVH if mild renal dysfunction is detected. Importantly, even in the lowest tertile of systolic BP (≤117 mm Hg), mild renal dysfunction tended to be associated with LVH, illustrating an independence of BP. Nonetheless, in this study, the risk accumulated with increasing BP (Fig. 2).

**Study Limitations**

This study provides cross-sectional observational data and therefore can be used only to generate new hypotheses. Because of the epidemiologic nature of the study, no clinical data or data about known predictors of LVH such as valve disorders or presence of myocardial infarction were obtained. We used electrocardiograms rather than echocardiograms to identify subjects with LVH. Therefore, the possibility exists that several cases of LVH were not detected or were falsely identified.

The strong points of this study, however, are the large size of the population, the reliable means of measuring microalbuminuria by two 24-h urine collections, and the computerized electrocardiographic analysis, which avoided intra- and interobserver bias.

In conclusion, our study shows that, in this large population, subjects with mild renal dysfunction have a higher prevalence of LVH on electrocardiography than those without renal dysfunction. We hypothesize that this find-

![Table of Odds Ratios](https://academic.oup.com/ajh/article-abstract/18/3/342/160758)

**FIG. 3.** Odds ratios of mild renal dysfunction for left ventricular hypertrophy (LVH) in prespecified subgroups. Odds ratios from multivariate analysis in each subgroup are shown, adjusted for age, sex, diabetes, myocardial infarction, systolic blood pressure (Syst.BP), diastolic blood pressure (Diast.BP), and antihypertensive medication.
ing may in part explain the increased risk for cardiovascular morbidity and mortality observed in subjects with mild renal dysfunction.

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