Relation of Left Ventricular Hypertrophy With Systemic Inflammation and Endothelial Damage in Resistant Hypertension

Gil F. Salles, Roberto Fiszman, Claudia R.L. Cardoso, Elizabeth S. Muxfeldt

Abstract—The relation between left ventricular hypertrophy (LVH) and unfavorable cardiovascular prognosis may involve systemic inflammation and endothelial dysfunction/damage. The aim of this study was to investigate in a cross-sectional design the relationships of LVH with C-reactive protein (CRP) levels (a marker of systemic low-grade inflammation) and with microalbuminuria (a marker of glomerular endothelial damage) in 705 patients with resistant hypertension. At baseline, all were submitted to a laboratory evaluation including 24-hour urinary albumin excretion, 2D echocardiogram, and 24-hour ambulatory blood pressure monitoring. A total of 463 patients also had high-sensitivity CRP levels determined. LVH was defined as an indexed left ventricular mass >110 g/m² in women and >125 g/m² in men. Microalbuminuria was evaluated in 3 categories: low normal (<15 mg/24 hours), high normal (between 15 and 29 mg/24 hours), and abnormal (between 30 and 299 mg/24 hours). CRP was dichotomized at the median value (3.7 mg/L).

Associations with LVH were examined after adjustment for all of the potential confounders by multivariate logistic regression. A total of 534 patients (75.7%) had LVH. After full adjustment, both abnormal microalbuminuria (odds ratio: 1.97; 95% CI: 1.04 to 3.73) and high CRP (OR: 1.76; 95% CI: 1.06 to 2.93) were independently associated with LVH occurrence. The high-normal albuminuria was associated with a borderline significant 46% increased chance of having LVH. Furthermore, the association between high CRP and LVH was observed exclusively in the subgroup with normal albuminuria. In conclusion, both systemic inflammation and endothelial damage were associated with LVH occurrence. These relationships offer insight into the pathophysiological mechanisms linking LVH to atherosclerosis and to increased cardiovascular morbidity and mortality. (Hypertension. 2007;50:000-000.)

Key Words: cardiovascular risk ■ C-reactive protein ■ left ventricular hypertrophy ■ microalbuminuria

Left ventricular hypertrophy (LVH) is a hypertensive target organ damage strongly predictive of future cardiovascular morbidity and mortality. However, the pathophysiologic mechanisms underlying the evolution from LVH to cardiovascular event development are still unclear, but they may involve accelerated atherosclerosis because of systemic inflammation and endothelial dysfunction.

C-reactive protein (CRP), a marker of chronic low-grade systemic inflammation, is a predictor of untoward cardiovascular prognosis, beyond traditional risk factors, in different populations. Also, its levels are generally elevated in patients with hypertension, and high CRP may even precede and predict the development of arterial hypertension.

Similarly, microalbuminuria (MA), a slight elevation of urinary albumin excretion rate (UAER), reflects endothelial dysfunction/damage at the glomerulus and possibly also systemically and is a risk marker for renal damage and cardiovascular morbidity/mortality in diabetic patients, in hypertensive individuals, and in general populations. It is frequently associated with other hypertensive target organ damage, particularly with LVH, and with diffuse atherosclerotic vascular disease.

Therefore, understanding the relationships between LVH and markers of low-grade systemic inflammation and endothelial dysfunction/damage is clinically and prognostically important. We hypothesized that the known association between LVH and MA may, at least in part, be mediated by systemic inflammation. So, the objective of this study was to evaluate in patients with resistant hypertension, a subgroup of general hypertensive subjects with a high cardiovascular risk profile, the relationships of the presence of LVH with CRP levels, a marker of systemic inflammation, and with MA and, particularly, to investigate whether MA, as reflecting endothelial damage, affects the association between LVH and inflammation.

Methods

This was a cross-sectional study within a cohort of resistant hypertensive patients enrolled from January 2000 to December 2006 in the hypertension outpatient clinic of our university hospital. All of the participants gave written informed consent and the local ethics committee had previously approved its protocol. The characteristics of this cohort, as well as its enrollment criteria, baseline protocol, and diagnostic definitions, have been detailed previously. In
TABLE 1. Baseline Characteristics of Resistant Hypertension Patients With and Without Echocardiographic LVH

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Normal LVMI (n=171)</th>
<th>Echo-LVH (n=534)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male, %</td>
<td>28.7</td>
<td>27.5</td>
<td>0.85</td>
</tr>
<tr>
<td>Age, y</td>
<td>64.0 (10.6)</td>
<td>65.2 (11.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.3 (5.6)</td>
<td>30.1 (5.7)</td>
<td>0.08</td>
</tr>
<tr>
<td>Abdominal circumference, cm</td>
<td>99.1 (11.4)</td>
<td>100.6 (12.1)</td>
<td>0.17</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>43.9</td>
<td>39.4</td>
<td>0.32</td>
</tr>
<tr>
<td>Coronary heart disease, %</td>
<td>18.2</td>
<td>28.1</td>
<td>0.011</td>
</tr>
<tr>
<td>Office SBP, mm Hg</td>
<td>175.8 (28.3)</td>
<td>180.5 (29.2)</td>
<td>0.07</td>
</tr>
<tr>
<td>Office DBP, mm Hg</td>
<td>96.8 (18.8)</td>
<td>97.3 (19.8)</td>
<td>0.79</td>
</tr>
<tr>
<td>24-hour SBP, mm Hg</td>
<td>131.4 (16.3)</td>
<td>139.0 (19.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-hour DBP, mm Hg</td>
<td>75.8 (11.7)</td>
<td>79.0 (13.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>24-hour PP, mm Hg</td>
<td>55.6 (12.1)</td>
<td>58.0 (13.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine, μmol/L</td>
<td>80 (71–97)</td>
<td>80 (71–98)</td>
<td>0.52</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.58 (1.29)</td>
<td>5.53 (1.25)</td>
<td>0.61</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.21 (0.31)</td>
<td>1.20 (0.35)</td>
<td>0.87</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.83 (1.08)</td>
<td>1.77 (1.17)</td>
<td>0.50</td>
</tr>
<tr>
<td>Microalbuminuria, mg/24 h</td>
<td>14.1 (7.3 to 27.9)</td>
<td>19.2 (9.9 to 59.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Microalbuminuria ≥15 and &lt;30 mg/24 h, %</td>
<td>22.2</td>
<td>24.9</td>
<td>0.09</td>
</tr>
<tr>
<td>Microalbuminuria ≥30 mg/24 h, %</td>
<td>24.6</td>
<td>34.8</td>
<td>0.003</td>
</tr>
<tr>
<td>CRP, mg/L*</td>
<td>3.1 (1.6 to 6.4)</td>
<td>4.2 (2.1 to 7.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>CRP ≥3.7 mg/L, %</td>
<td>39.2</td>
<td>53.6</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Values are means (SD) or proportions, except * median (interquartile range). LVMI indicates left ventricular mass indexed to body surface area; Echo-LVH, echocardiographic LVH; PP, pulse pressure; HDL, high density lipoprotein.

Statistical Analysis

Continuous data were described as means and SDs for those with normal distribution and as medians and interquartile ranges for asymmetrically distributed data. Bivariate comparisons between patients with and without LVH were performed by unpaired t tests in continuous normally distributed data, by nonparametric Mann-Whitney test in asymmetrically distributed data, or by χ² test in categorical data. Correlation between MA and CRP was assessed by nonparametric Spearman’s rank coefficient of correlation. Associations of LVH with MA and CRP were investigated by multivariate logistic regression, with LVH as the dependent variable. First, each independent variable (MA: 3 categories, reference: the low-normal subgroup; and CRP: 2 categories, reference: the below the median subgroup) was tested isolated, adjusted for age and gender, and after full adjustment for all of the potential variables that could influence LVH (age, gender, waist circumference, body mass index [BMI], presence of diabetes and coronary heart disease at baseline, all anti-hypertensive drug treatment, 24-hour SBP and pulse pressure, serum lipids, and creatinine). Second, the logistic regression was repeated, entering both variables simultaneously into the model, again after initial adjustment for age and gender and then after full adjustment. Interaction terms between MA and CRP subgroups were tested and, because there was a borderline significant interaction between CRP and the abnormal MA subgroup, a subgroup analysis stratified by MA status was also undertaken. All of the statistics were performed by SPSS version 13.0, and a 2-tailed P<0.05 was regarded significant.

brief, all of the referred subjects with resistant hypertension (defined by office blood pressure [BP] ≥140/90 mm Hg using ≥3 antihypertensive drugs in full dosages always including a diuretic) were submitted to a standard protocol that included a complete clinical examination, laboratory evaluation, 24-hour ambulatory BP monitoring, and every 30 minutes at night. Parameters evaluated were average 24-hour SBP, DBP, and pulse pressure (PP), calculated as 24-hour SBP minus DBP. 2D transthoracic echocardiography (Siemens, Sonoline G60S) was performed by the same experienced observer. Its methods have been described previously.15 Left ventricular mass was calculated by the formula of Devereux and Reichek16 and indexed to body surface area. The diagnosis of LVH was defined by left ventricular mass indexed to body surface area >125 g/m² in men and >110 g/m² in women.

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Results
LVH was diagnosed in 534 patients (75.7%). Table 1 shows the baseline characteristics of patients with and without LVH. Patients with LVH had a slightly higher BMI, higher prevalence of coronary heart disease, higher office and 24-hour BPs, and higher UAER and CRP levels than patients without LVH. Patients without CRP measurement at baseline had characteristics identical to those who had CRP levels determined (data not shown), including the prevalences of LVH (75.9% versus 75.5%, respectively; \( P = 0.93 \)) and of abnormal MA (34.3% versus 29.8%, respectively; \( P = 0.12 \)).

Table 2 shows the isolated associations of CRP and MA with LVH. Both variables were independently associated with LVH. After full adjustment for other potential confounders, the high (above the median) CRP subgroup of patients had a 70% greater chance of having LVH than the low CRP group, whereas the abnormal MA subgroup showed an 80% increased chance of LVH occurrence in relation to the reference low-normal MA subgroup. Patients in the high-normal MA subgroup presented a borderline significant 50% higher risk of having LVH than the low-normal group. When entered concomitantly into the same logistic model analysis, both variables, high CRP and abnormal MA, remained significantly associated with LVH, even after full adjustment (Table 3). In this analysis, the interaction term between the high CRP and abnormal MA subgroups was of borderline significance (\( P = 0.10 \)), suggesting the possibility of effect modification according to different categories of MA. Thus, a subgroup analysis was performed stratified by normal or abnormal MA status (Table 4). After full adjustment, a high CRP was strongly associated with LVH only in the subgroup of patients with normal MA (<30 mg/24 h), with an \( \approx 2.5 \)-fold greater chance of LVH in the high CRP group in comparison with the low CRP group. In the abnormal MA subgroup of patients, a nonsignificant inverse association between high CRP and LVH occurrence was found.

Discussion
The main finding of this study is that both low-grade chronic inflammation, estimated by high CRP levels, and endothelial dysfunction/damage, reflected by MA, are associated with LVH occurrence in patients with resistant hypertension, independent of several other important covariates, such as adipose tissue distribution (BMI and waist circumference),

<table>
<thead>
<tr>
<th>Variables</th>
<th>Model A*</th>
<th></th>
<th>Model B‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP ( \geq 3.7 \text{ mg/L} )</td>
<td>2.03 1.31 to 3.15 0.002</td>
<td>1.71 1.07 to 2.75 0.025</td>
<td></td>
</tr>
<tr>
<td>MA ( &lt;15 \text{ mg/24 h} )</td>
<td>1.52 0.98 to 2.35 0.06</td>
<td>1.46 0.92 to 2.31 0.10</td>
<td></td>
</tr>
<tr>
<td>( \geq 15 \text{ and } &lt;30 \text{ mg/24 h} )</td>
<td>2.01 1.32 to 3.06 0.001</td>
<td>1.81 1.14 to 2.89 0.013</td>
<td></td>
</tr>
</tbody>
</table>

OR indicates odds ratio.
*Model A was adjusted for age and gender.
‡Model B was adjusted for age, gender, waist circumference, BMI, presence of diabetes and coronary heart disease at baseline, 24-hour systolic and pulse pressures, antihypertensive drug treatment, serum creatinine, total cholesterol, high-density lipoprotein cholesterol, and triglycerides.
hemodynamic factors (24-hour BP levels on ambulatory BP monitoring), presence of diabetes and coronary heart disease, serum lipids, renal function, age, and gender. Furthermore, we demonstrate that the association between CRP and LVH is observed only in the subgroup with normal UAER. As far as we know, these findings are new and potentially important for understanding the pathophysiological mechanisms linking LVH to atherosclerosis and to increased cardiovascular morbidity and mortality.

LVH and MA represent well-known subclinical markers of increased incidence of cardiovascular events. Many authors believe that CRP levels may be yet another important marker for the development of cardiovascular disease, although others did not corroborate these findings. The amount and quality of the available evidence indicate that CRP must have some importance, but the magnitude and the mechanisms of its effects are still unsettled. Several previous reports have established a consistent association between MA and LVH in hypertensive subjects, as well as in diabetic patients and in general populations. Otherwise, only 2 previous cross-sectional studies have specifically assessed the relationships among LVH, MA, and CRP, with somewhat different findings. Palmieri et al. in 1299 type 2 diabetic individuals, showed that the association of echocardiographic LVH with 2 markers of inflammation and atherothrombosis (CRP and fibrinogen) was abolished when the influence of BMI and MA was taken into account, suggesting that the association between LVH and inflammation was mainly mediated by microangiopathy/endothelial dysfunction and obesity. Our results oppose these findings in that only a small nonsignificant attenuation of the association between elevated CRP and LVH was observed after adjustment for body fat distribution (waist circumference to account for abdominal obesity in addition to BMI); odds rates changed from 1.99 to 1.85 (data not shown). The most plausible explanation is that obesity is a much more important confounding covariate in the relationships between LVH and inflammation in type 2 diabetes than it is in hypertensive patients. The second study, in 220 never-treated hypertensive nondiabetic men, in agreement with our results, observed a significantly higher prevalence of concentric LVH in the subgroup with both abnormal MA and elevated CRP, although the interrelations of CRP and MA with LVH were not further investigated.

No attenuation of the strength of the association between LVH and MA was found after further adjustment for CRP levels (this can be ascertained by the virtually unchanged odds ratios associated with abnormal MA from Table 2 to Table 3: 2.01 and 1.81 to 1.98 and 1.97). Otherwise, interaction between CRP and abnormal MA was revealed, and the major influence of systemic inflammation on LVH was observed exclusively in the subgroup of patients with normal UAER (Table 4). This finding contrasts with our initial hypothesis that at least part of the known association between MA and LVH might be mediated by systemic inflammation but raises some mechanistic possibilities for this lack of association between CRP and LVH in microalbuminuric patients. Although in cross-sectional studies no inferences on temporal or causal relationships can be made, the association between CRP and LVH, seen only in the subgroup with normal UAER, suggests that systemic low-grade inflammation might precede endothelial dysfunction/damage. At the initial stage of the atherosclerotic process, systemic inflammation would appear most importantly associated with subclinical cardiovascular disease development, such as LVH occurrence. Later in the course of atherosclerosis, when systemic endothelial damage has resulted, MA would become most strongly associated with cardiovascular disease and the importance of systemic inflammation on LVH occurrence would decrease. This pathophysiological sequence of events is supported by previous prospective studies demonstrating that high CRP levels preceded and were determinants of MA development and progression in type 2 diabetic patients and in a population-based sample. These speculations about the temporal and causal relationships among systemic inflammation, endothelial damage, and LVH occurrence and progression are clinically and prognostically relevant and should be addressed in future prospective longitudinal studies.

Patients in the high-normal MA subgroup (UAER between 15 and 29 mg/24 h) presented a borderline significant 50% increased risk of having LVH than patients in the low-normal MA range (<15 mg/24 h), after adjustment for all potential confounders (Table 2), corroborating with recent reports suggesting that UAER values below the traditional cutoff for abnormal MA are still associated with increased cardiovascular risk and with the risk of developing arterial hypertension.

We do not find any correlation between UAER and CRP levels. This lack of association has been reported by some but not by other investigations, and it has also been suggested that their association may be influenced by BP levels, being positive only in hypertensive subjects.

### Table 4: Multivariate Logistic Regression for Associations Between Echocardiographic LVH (the Dependent Variable) and CRP According to Different Urinary Albumin Excretion Levels

<table>
<thead>
<tr>
<th>Variable, CRP ≥3.7 mg/L</th>
<th>MA &lt;30 mg/24 h (n=325)</th>
<th>MA ≥30 mg/24 h (n=138)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI P</td>
<td>OR 95% CI P</td>
</tr>
<tr>
<td>Model A*</td>
<td>2.53 1.46 to 4.09 0.001</td>
<td>0.96 0.36 to 2.58 0.94</td>
</tr>
<tr>
<td>Model B†</td>
<td>2.43 1.36 to 4.35 0.003</td>
<td>0.45 0.12 to 1.63 0.22</td>
</tr>
</tbody>
</table>

OR indicates odds ratio.
*Model A was adjusted for age and gender.
†Model B was adjusted for age, gender, waist circumference, BMI, presence of diabetes and coronary heart disease at baseline, 24-hour systolic and pulse pressures, antihypertensive drug treatment, serum creatinine, total cholesterol, high-density lipoprotein cholesterol, and triglycerides.
mean arterial pressure >90 mm Hg). Because CRP and MA are thought to reflect closely related components of the atherosclerotic process (the state of low-grade inflammation of the arterial vessel wall and the endothelial damage at the glomerulus and also systemically), this lack of association is unexpected but helps to explain their independent predictive values for future cardiovascular morbidity and mortality.23,26 Also, it has been demonstrated14 that CRP and MA are independently associated with different domains of atherosclerotic vascular disease. These observations suggest that CRP and MA may reflect different pathophysiological mechanisms leading to subclinical cardiovascular disease, including LVH, and, finally, to morbidity cardiovascular events.

Some limitations of this study are important to note. First, as pointed out previously, the cross-sectional design prevents the demonstration of the mechanisms by which LVH is related to albuminuria and inflammation. The temporal and causal inferences raised about the pathophysiological process underlying these relationships must be regarded as merely speculative. Second, the measurement of UAER was based on a single 24-hour urine collection. Although this method is considered preferred instead of urinary albumin/creatinine ratio in a morning spot, some misclassification of MA may have occurred because of incompletely collected samples or random albuminuria fluctuation. Three nonconsecutive 24-hour urine collections would have been the best method. However, misclassification is likely to weaken the demonstrated relationships, suggesting that true associations may, in fact, be stronger. Finally, this study evaluated patients with resistant hypertension, a common but somewhat understudied subgroup of general hypertensive subjects, with a high prevalence of LVH. So, our results may not be generalized to other less severe hypertensive subjects.

Perspectives
This study provides evidence that LVH is associated independently with chronic low-grade systemic inflammation, reflected by elevated CRP levels, and with endothelial dysfunction/damage, reflected by abnormal MA, in patients with resistant hypertension. Moreover, the impact of inflammation appears to reside mainly in patients with normal albuminuria. These relationships offer insight into the pathophysiologic mechanisms that link LVH occurrence with the atherosclerotic process and with cardiovascular morbidity and mortality. Prospective studies are necessary to answer important questions regarding the temporal and causal relations of LVH development and progression with markers of systemic inflammation and MA, as well as their independent roles in cardiovascular risk stratification.

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Disclosures
None.

References


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