Comparison of Target Organ Damage in Renovascular and Essential Hypertension

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In many reports, the prevalence of target organ damage in renovascular hypertension (RVH) appears to be higher than in essential hypertension (EH). Since in most studies the renal artery stenosis is part of a diffuse atherosclerotic disease, it is not known whether these complications are due to RVH itself or to the vascular disease.

We have undertaken a case control study of 92 patients divided into two groups (46 in each), one with RVH and the other with EH and abdominal aortic aneurysm, with a comparable degree of diffuse atherosclerotic vascular disease. The vascular state of the extracranial carotid arteries and abdominal and inferior limb districts was investigated with angiography and sonography. The prevalence of left ventricular hypertrophy (LVH) and ischemic heart disease (IHD) were assessed by electrocardiography. Serum creatinine and urinary protein excretion were employed in the renal evaluation. While the analysis of the results confirmed an even diffusion of atherosclerotic vascular disease between the two groups, a significant difference was found in the prevalence of heart and renal damage. LVH was present in 32.6% of RVH patients versus 10.8% in EH \( (P = .02) \). Serum creatinine > 1.4 mg/dL was found in 50% of RVH and in 23.9% of EH, \( (P = .01) \). The prevalence of proteinuria in RVH was also higher although not reaching the statistical significance. The results suggest that, in patients with comparable degrees of atherosclerotic vascular disease, RVH is responsible for the higher prevalence of target organ damage in this condition compared to those with EH. Am J Hypertens 1996;9:1062–1067

KEY WORDS: Renovascular hypertension, end-organ damage, atherosclerotic vascular disease.

It is generally accepted that patients with hypertension of renovascular origin (RVH) have a more severe disease, and are more prone to developing cardiovascular involvement than those with essential hypertension (EH).\(^1\)-\(^3\) A high prevalence of left ventricular dysfunction, a major marker of cardiovascular morbidity and mortality, has been reported in RVH.\(^4\)-\(^5\) Pairwise, reports about renal function in RVH point to a high prevalence of renal impairment.\(^6\)-\(^7\) Most clinical studies that support these assumptions are based on comparisons made between patients with renal artery stenosis of both atheromatous and nonatheromatous (fibromuscular dysplasia) origin and patients with uncomplicated EH. Therefore, it is difficult to distinguish the role played by the specific mechanisms activated by RVH from the independent role played by the diffuse atherosclerotic vascular disease in causing target organ damage. This is particularly true in older patients in whom the renin-angiotensin system does not appear to be a major factor in the genesis of high peripheral resistance and its end-organ consequences.\(^8\)

On the other hand, an excess prevalence of atherosclerotic vascular lesions has been shown in patients
with RVH, and this secondary abnormality may also cause renal and cardiovascular complications. However, no systematic investigation aimed at singling out the harmful role of diffuse atherosclerotic vascular disease in the context of RVH has been carried out.

Both electrocardiographic (ECG) and echocardiographic left ventricular hypertrophy (LVH) are major risk factors for cardiovascular mortality. In this cross-sectional case-control study, we investigated the prevalence of ECG-LVH, coronary heart disease, and renal damage in patients with atherosomatous RVH and diffuse vascular disease in comparison with EH patients with comparable atherosclerotic vascular disease. Furthermore, several known risk factors were taken into account in the study design and in the analysis of results.

PATIENTS AND METHODS

Study Population Forty-six consecutive patients with RVH of atheromatous origin and diffuse atherosclerotic vascular changes were enrolled in the study. Patients were studied while attending the vascular surgery unit for diagnostic or therapeutic procedures concerning their vascular disease; most of them were unaware of their renal artery stenosis before entering the hospital. Forty-six age-matched (within 3 years) EH patients with diffuse atherosclerotic vascular disease were the controls. RVH was excluded by a negative renal arteriogram, obtained during the diagnostic work-up for abdominal aortic aneurysm not involving renal arteries that had been previously detected by ultrasonography. All studied subjects were on antihypertensive treatment with one or more drugs when admitted to the hospital, at which time blood pressure was assessed by cuff sphygmomanometry following standard recommendations. Four RVH patients and seven controls were diabetic. Routine screening tests were employed to rule out the presence of other forms of renal disease. The characteristics of subjects enrolled in the present study are shown in Table 1.

Methods The diagnosis of RVH was made by angiography combined with captopril renography with Tc-DTPA (technetium-99m-diethylenetriamine pentaacetic acid). The angiographic study consisted in aortic, renal, abdominal and peripheral arteries digital subtraction angiography performed according to standard techniques with particular interest in an optimal evaluation of renal arteries. The degree of renal arteries narrowing was expressed in percentage of the lumen occluded for each artery studied both in unilateral and bilateral stenosis; only patients with stenosis ≥ 65% were enrolled in the study.

The captopril renography was performed after discontinuation of antihypertensive drugs, keeping the patients on moderately restricted sodium intake (2 to 3 g/24 h). For the interpretation of the test, the recommendations of Mann et al were followed. The renal scan confirmed the angiographic diagnosis in all RVH patients.

The atherosclerotic vascular disease of abdominal district and limbs was assessed by angiography. Arterial involvement was scored on an arbitrary scale (0 to 3 for limb arteries; 0 to 4 for abdominal arteries) taking into account the number of the involved vessels and the degree of the narrowing.

The sonographic examination of extracranial artery was carried out by an expert operator (PDR) unaware of the presence of RAS. Extracranial carotid arteries were assessed by color flow echo Doppler (color-duplex scanner Aloka SSD 680, with a linear probe 7.5 MHz). Common carotid artery, internal carotid artery, and external carotid artery were evaluated by the analysis of the B-mode imaging, the Doppler signal, and the code color signal. The B-mode study was employed for the study of the arterial wall, particularly aimed at the plaque assessment (ie, low acoustic density plaque or echotranslucent, high acoustic density plaque or echogenic, homogeneous plaque, ulcerous plaque, etc). The sonographic study included the vertebral-subclavian district.

Carotid artery lesions were scored on an arbitrary scale as follows: negative = 0, isolated unilateral stenosis with lumen narrowing < 80% = 2, unilateral stenosis > 80% = 4, bilateral disease with at least one stenosis > 80% = 5.

Complete blood chemistry, including serum cholesterol and triglycerides, was performed in all subjects. Plasma creatinine and urinary protein excretion were performed in the assessment of renal damage, and were determined as previously described. A value of plasma creatinine > 1.4 mg/dL was taken as an index of renal functional impairment.

Standard 12-lead electrocardiogram (ECG) was performed in all subjects in the vascular surgery ward and sent, without diagnosis and clinical notes, to one of us (LZ) working in another hospital for a blind interpretation. The diagnosis of LVH was made by an improved method that combined three highly specific criteria. This method had been previously validated by a comparison study with echocardiographic measurement of left ventricular mass; the sensitivity was shown to be 39% and specificity 94% with a positive predictive value of 71% (95% CI 63% to 78%).

Statistical analysis was performed on a computer using the BMDP package (BMDP Statistical Software, Cork, Ireland). For normally distributed data mean, standard deviation and 95% confidence intervals were calculated. Comparisons were made with the Student's t test. Ordinal data and proportions were compared with the Fisher's exact test, Mann-Whitney U test, and odds ratio.

RESULTS

Renal artery stenosis was bilateral in 5 patients and unilateral in the remaining 41 with an average nar-
TABLE 1. CLINICAL CHARACTERISTICS AND BIOCHEMICAL PARAMETERS IN STUDIED SUBJECTS

<table>
<thead>
<tr>
<th></th>
<th>RVH</th>
<th>EH</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>46</td>
<td>46</td>
<td>0</td>
</tr>
<tr>
<td>Age (years)</td>
<td>69.0 ± 6.4</td>
<td>71.6 ± 6.4</td>
<td>2.06 (–0.01–5.35)</td>
</tr>
<tr>
<td>Sex (m/f)</td>
<td>38/8</td>
<td>44/2</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)*</td>
<td>162.1 ± 17.6</td>
<td>151.7 ± 18.0</td>
<td>10 (1.9–18.8)</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)*</td>
<td>88.9 ± 8.8</td>
<td>86.2 ± 11.0</td>
<td>3 (–2.1–3.1)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.63 ± .79</td>
<td>1.32 ± .36</td>
<td>0.31 (0.05–0.5)</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>218.8 ± 46.2</td>
<td>216.0 ± 47.2</td>
<td>2.07 (–22.6–17.1)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>149.0 ± 93.4</td>
<td>145.2 ± 91.7</td>
<td>3.07 (–46.0–38.4)</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>101.3 ± 22.5</td>
<td>95.7 ± 22.5</td>
<td>5.05 (–21.3–10.2)</td>
</tr>
</tbody>
</table>

RVH, Renovascular hypertension; EH, essential hypertension. Values are expressed as mean ± SD. The differences of the mean are given with 95% confidence intervals.

* Patients on antihypertensive treatment.

rowling of 77.7 ± 17%. In three patients a complete occlusion of one renal artery was present.

Systolic blood pressure was higher in RVH patients than in controls (162.1 ± 17.8 mm Hg v 151.7 ± 18.3 mm Hg; t = 2.35, P = .016), while diastolic values were comparable (Table 1). The number of antihypertensive drugs, per patient, necessary to keep BP under control was 1.95 ± 0.94 in RVH and 1.42 ± 0.57 in EH (t = 2.75; P = .007). The classes of agent employed were calcium channel antagonists (RVH 50%, EH 60%), diuretics (RVH 54.4%, EH 38.4; Fisher’s exact test P = .02), angiotensin converting enzyme inhibitors (ACEI) (RVH 31.8%, EH 23.9%), adrenoceptor antagonists (RVH 13.6%, EH 6.5%), clonidine (RVH 6.8%, EH 0), and peripheral vasodilators (RVH 4.5%, EH 8.6%).

Diffuse atherosclerotic vascular disease was present in both groups with an equal distribution (Table 2). The statistical comparison showed a similar prevalence of disease for the three vascular district examined (extracranial carotid, abdominal and limb arteries) in RVH and EH patients.

Clinical and electrocardiographic manifestations of ischemic heart disease (IHD) were found in 28% of RVH patients and in 15% of EH (difference not significant). Table 3 shows the data and the statistics pertinent to heart and kidney damage in both groups of patients.

ECG-LVH was found in 15 patients with RVH (32.6%) and in 5 (10.8%) with EH. The difference was significant (Fisher’s exact test P = .02). Systolic blood pressure in RVH patients with LVH was 156.2 ± 16.1 mm Hg and in those without LVH was 164.8 ± 18.2 mm Hg. LVH was present in 12 (29.2%) patients with unilateral renal artery stenosis and the difference with EH was also significant (Fisher’s exact test P = .05). No association was found between treatment with specific antihypertensive agents and the prevalence of LVH.

Serum creatinine was higher in RVH than in controls (1.63 ± 0.79 mg/dL v 1.32 ± 0.36 mg/dL; the 95% CI of the difference was 0.050 to 0.576; t = 2.148, P = .01). In unilateral renal artery stenosis the serum creatinine was 1.60 ± 0.78 mg/dL (the significance of the difference with EH was: t = 2.13, P = .03). The prevalence of a creatinine > 1.4 mg/dL was 50% in RVH and 23.9% in EH (Fisher’s exact test P = .01). In RVH patients with serum creatinine > 1.4 mg/dL systolic BP was 154.2 ± 20.6 mm Hg; in those with creatinine < 1.4 mg/dL systolic BP was 168.6 ± 14.7 mm Hg (differ-

TABLE 2. PREVALENCE AND DEGREE OF ARTERIAL DISEASE IN RVH PATIENTS AND EH CONTROLS

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Total of lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pts. (%)</td>
<td>Pts. (%)</td>
<td>Pts. (%)</td>
<td>Pts. (%)</td>
<td>Pts. (%)</td>
<td>Pts. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Carotid artery*</td>
<td>RVH 17 (36.9%)</td>
<td>5 (10.8%)</td>
<td>1 (2.17%)</td>
<td>20 (43.4%)</td>
<td>3 (6.6%)</td>
<td>0 (0%)</td>
<td>29 (63%)</td>
</tr>
<tr>
<td></td>
<td>EH 14 (30.4%)</td>
<td>9 (19.5%)</td>
<td>0 (0%)</td>
<td>20 (43.8%)</td>
<td>2 (4.35%)</td>
<td>1 (2.17%)</td>
<td>32 (69.6%)</td>
</tr>
<tr>
<td>Abdominal artery†</td>
<td>RVH 6 (13.0%)</td>
<td>13 (28.2%)</td>
<td>5 (10.8%)</td>
<td>21 (45.6%)</td>
<td>1 (2.1%)</td>
<td>40 (87%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EH 4 (8.7%)</td>
<td>18 (39.1%)</td>
<td>4 (8.7%)</td>
<td>20 (43.4%)</td>
<td>0 (0%)</td>
<td>42 (91.3%)</td>
<td></td>
</tr>
<tr>
<td>Limb artery‡</td>
<td>RVH 8 (17.3%)</td>
<td>10 (21.7%)</td>
<td>3 (6.5%)</td>
<td>25 (54.3%)</td>
<td>38 (82.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>EH 6 (13.4%)</td>
<td>20 (43.4%)</td>
<td>3 (6.5%)</td>
<td>17 (36.9%)</td>
<td>40 (86.6%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 0–5 scale
† 0–4 scale
‡ 0–4 scale RVH, Renovascular hypertension; EH, essential hypertension.
TABLE 3. PREVALENCE OF HEART AND KIDNEY DAMAGE IN RVH AND EH

<table>
<thead>
<tr>
<th></th>
<th>RVH</th>
<th>EH</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>zValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>number</td>
<td>46</td>
<td>46</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVH</td>
<td>32.60%</td>
<td>10.80%</td>
<td>3.96</td>
<td>1.3–12.0</td>
<td>2.726</td>
</tr>
<tr>
<td>IHD</td>
<td>28%</td>
<td>15%</td>
<td>2.19</td>
<td>0.78–6.11</td>
<td>1.555</td>
</tr>
<tr>
<td>Creatinine &gt; 1.4 mg/dL</td>
<td>50%</td>
<td>24%</td>
<td>3.18</td>
<td>1.29–7.70</td>
<td>2.679</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>65.70%</td>
<td>47.60%</td>
<td>2.11</td>
<td>0.93–5.15</td>
<td>2.115</td>
</tr>
</tbody>
</table>

RVH, Renovascular hypertension; EH, essential hypertension; LVH, Left ventricular hypertrophy; IHD, Ischemic heart disease.

Diastolic BP was comparable. RVH patients treated with ACE inhibitors (n = 14) had a creatinine of 1.46 ± 0.26 mg/dL; in those treated with other drugs it was 1.71 ± 0.92 mg/dL (difference not significant). No association was found between high serum creatinine and LVH.

Urinary protein excretion was 630 ± 1260 mg/24 h in RVH and 375 ± 1140 mg/24 h in EH (not significant). A proteinuria > 300 mg/24 h was found in 30 patients with RVH and in 21 with EH (Table 3). The presence or the values of urinary protein were not correlatable with serum creatinine or with the presence of LVH in either groups.

DISCUSSION

Our study demonstrates that in patients with atherosclerotic vascular disease, the presence of renovascular hypertension is associated with a more severe target organ damage than in essential hypertension.

The 32% prevalence of LVH is strikingly high, considering that ECG provides a crude measure of ventricular mass. In elderly people the level of systolic BP is more highly correlated with subsequent cardiovascular morbidity than is diastolic BP. In our RVH patients systolic BP, on antihypertensive treatment, was higher than in EH controls, but within the group itself no association was found between high systolic BP and LVH. Sound data on blood control during the previous years was lacking for both groups and this has hampered us in gaining a deeper insight into this important aspect of the problem. Therefore, we cannot rule out that differences in BP occurred during previous years could be responsible for the differing prevalences in LVH we found.

In our study cardiac involvement was assessed clinically and by ECG. This investigation was chosen, in spite of its relative limitations, for practical reasons (easy to perform, therefore reduced hospital stay during diagnostic work-up). ECG was also considered for its easier standardization of LVH criteria, and its capacity to provide important information not only on LVH but also on other types of cardiac abnormality that might be relevant. Furthermore, for these and other advantages, ECG is still widely employed in epidemiological studies.

Previous studies had shown a high prevalence of severe atherosclerotic arterial disease in patients with RVH. Therefore, when comparing the harmful effects of RVH with those of EH the role of this vascular process causing organ damage must be ruled out. To our knowledge studies aimed at this aspect have not been published. Although we had previously shown that patients with aortic aneurysm are at risk of renal dysfunction also in absence of stenosis of renal arteries, we chose these patients as a control group for the presence of the atherosclerotic disease, and because renal angiography was part of the routine diagnostic work-up. This allowed us to positively rule out renal artery stenosis, while in most previous studies dealing with such comparisons, this exclusion was made only on clinical grounds, leaving some doubts, especially for older patients.

Since we found that in both groups of patients the degree of vascular involvement was comparable and atherosclerosis was equally distributed, the vascular disease could not be considered responsible for the difference in the end-organ complications. Thus, the cause of the higher prevalence of heart and kidney disease in RVH is to be ascribed to factors other than the diffuse atherosclerotic process. We found RVH itself to be the major distinctive element in the two observed populations. Therefore, the cause of the more severe renal and cardiac damage in this group of hypertensive patients in comparison with controls can be considered related to this process.

There are many complex mechanisms activated by RVH that could lead to heart disease and renal dysfunction. Heart disease in patients with hypertension has been associated with high renin profile also in absence of renal artery stenosis. Conversely, an altered left ventricular contractility and a maladaptive response to increased pressure load was found in patients with RVH with high renin levels. Likewise, studies in the experimental animal have indicated that angiotensin II may, at least in part, mediate the stretch-induced hypertrophic growth of cardiomyocytes, via the type 1 angiotensin receptor. Therefore, although only circumstantial, most of the evidence points to the renin-angiotensin system as responsible for heart involvement in RVH. In our patients a mea-
measure of renin was not performed regularly, but we considered the hemodynamic response to captopril in the DTPA renography as a strong indirect evidence of its activation.25

In this study, renal damage in RVH patients with unilateral renal artery stenosis is shown mostly by the abnormal serum creatinine, but we should also take into account the prevalence of proteinuria, although this was not statistically significant. This finding is in good keeping with previous reports that also showed a regression of proteinuria with the cure of RVH.26

Only 5 of our RVH patients had a bilateral disease where the severity of the stenosis could be responsible for the reduced renal function. In atherosclerotic unilateral renal artery stenosis, the ability of renal hemodynamics and function to adapt to reduced renal blood flow is maintained within large limits. Therefore, total glomerular filtration rate appears to depend largely on the contralateral nonstenotic kidney, and has been shown to be within the normal range unless complicated by parenchymal damage.27 Since our patients with unilateral stenosis and higher serum creatinine had blood pressure values comparable to those with normal creatinine, a difference in the harmful effect of hypertension on the contralateral kidney seems unlikely.

The most obvious pharmacological cause of functional renal impairment can be excluded in our RVH patients, since no association was found between ACEI therapy and high serum creatinine.28 Circumstantial evidence from experimental animals suggests that renin is vasculotoxic within the kidney itself.29 Its participation in causing renal damage in hypertensive elderly subjects predisposed by diffuse atherosclerotic disease can be reasonably accepted.

Glomerular hypertension and hyperfiltration in the contralateral kidney of a renal artery stenosis has been demonstrated in humans, and is also indicated as a cause of renal damage in this disease process.30 The presence of proteinuria in the presence of a normal renal function in hypertensive subjects is associated with glomerular hyperfiltration.31 Since in this study many proteinuric patients had a normal creatinine, we cannot exclude that this type of pathological mechanism also may operate in RVH.

In light of our results, considering that blood pressure values do not seem to be the only determinants of end-organ damage in RVH, we advocate a more radical therapeutic approach in these elderly patients to prevent such complications.

REFERENCES


