Carotid and Lower Extremity Arterial Disease in Patients With Renal Artery Atherosclerosis

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Background: Atherosclerotic lesions of the carotid and lower extremity arteries may be associated with renal artery stenosis and influence the management of patients with renal artery disease.

Objective: To document the prevalence and clinical features of carotid and lower extremity arterial disease in patients with renal artery atherosclerosis.

Methods: An analysis of baseline data on 149 patients enrolled in a prospective natural history study of atherosclerotic renal artery stenosis. Patients with at least 1 abnormal renal artery by duplex scanning were eligible. Carotid artery disease was evaluated by duplex scanning, and ankle/brachial indices were used to assess the lower extremity arteries. Disease at each of the 3 arterial sites was classified as mild, moderate, or severe based on the extent of involvement on both sides. Serum urea nitrogen, creatinine, and lipid levels were also measured.

Results: Severe renal, carotid, or lower extremity arterial disease was present in 44%, 19%, and 21% of the patients, respectively. There was a trend for patients with increasing degrees of renal artery disease to have increasing degrees of carotid and lower extremity arterial disease. The prevalence of severe carotid artery disease increased from 7% in the mild renal artery group to 28% in the severe renal artery group. Clinical factors that were most predictive of severe disease were elevated apolipoprotein B levels for the renal arteries, high serum urea nitrogen or creatinine levels for the carotid arteries, and smoking for the lower extremity arteries.

Conclusions: There was a strong association between severe renal artery atherosclerosis and severe carotid artery disease. Patients with renal artery disease also had a high prevalence of lower extremity arterial disease. In this patient population, screening for lower extremity arterial disease can be reserved for those with signs or symptoms of peripheral ischemia. Noninvasive carotid screening is justified in patients with renal artery disease to detect asymptomatic lesions that require either immediate surgical treatment or serial follow-up for disease progression.

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PATIENTS AND METHODS

STUDY DESIGN

A prospective study on the natural history of renal artery stenosis was initiated at the University of Washington Medical Center in January 1990, and recruitment of patients continued through 1997. Patients with suspected renal artery disease were obtained by referrals from physicians at the University of Washington Medical Center and surrounding communities. Indications for renal artery screening by duplex scanning are hypertension, decreased renal function, or both. Those patients who were found to have at least 1 abnormal renal artery and who were not considered candidates for immediate intervention were eligible for enrollment in the study. This study was approved by the Human Subjects Review Committee at the University of Washington and informed consent was obtained.

In addition to a complete renal artery duplex scan, clinical information obtained at the baseline and follow-up patient evaluations included risk factors for atherosclerosis (smoking, diabetes, serum lipid levels), symptoms or signs of atherosclerotic disease at other sites (coronary, carotid, and lower extremity arteries), and any interventions for the treatment of arterial disease. The duration and treatment of hypertension were also documented. Blood pressures were recorded in both arms, and the higher of the two arm’s blood pressure measurements was used in this analysis. Blood samples for serum urea nitrogen (SUN), creatinine, and lipid levels (total cholesterol, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], total triglycerides, apolipoprotein A-I [Apo A-I], lipoprotein(a) [Lp(a)], and apolipoprotein B [Apo B]) were obtained at each patient visit. Follow-up intervals in the natural history protocol were 6 months for those patients with at least one high-grade (≥60% diameter reduction) renal artery stenosis and 12 months for patients with less severe renal artery lesions.

To objectively document the degree of atherosclerotic involvement in the extracranial carotid and lower extremity arteries, carotid duplex scanning and measurement of ankle/brachial indices (ABIs) were added to the study protocol in January 1992. This report is a cross-sectional analysis of baseline visit data for 149 patients who had renal and carotid artery duplex scans and ABI measurements through May 1996. Serum lipid data were available for 129 of the 149 patients.

RENAL ARTERY DUPLEX SCANNING

The technique of renal artery duplex scanning used at the University of Washington has already been described.12-14 All examinations were performed with an ATL Ultramark 9 or HDI duplex ultrasound system (Advanced Technology Laboratories, Bothell, Wash). Patients were examined after an overnight fast using either a 2.25- or 3.2-MHz phased array or 3-MHz mechanical sector transducer. The abdominal aorta was evaluated initially to determine if there was aneurysmal of occlusive disease, and the aortic peak systolic velocity was measured at or above the level of the superior mesenteric artery. From a midline approach, the renal arteries were identified with the aorta in transverse view, and velocities were recorded along their entire lengths with particular emphasis on any focal areas of increased flow velocity or turbulence. The distal renal arteries, as well as the hilar and parenchymal flow patterns, were evaluated from a lateral decubitus or posterior approach if they were not adequately imaged transabdominally. The angle of the Doppler ultrasound beam was 60° or less for all renal artery velocity measurements.

The severity of stenosis in each renal artery was classified according to previously validated criteria based on artery atherosclerosis. The features of atherosclerotic involvement in these arterial segments were analyzed to address the following 3 questions: (1) Is there an association between atherosclerotic disease of the renal, extracranial carotid, and lower extremity arteries? (2) What clinical factors correlate with the severity of carotid and lower extremity atherosclerosis in patients with renal artery disease? and (3) What are the appropriate guidelines for screening carotid and lower extremity arterial disease in patients presenting with renal artery stenosis?

RESULTS

Among the 149 patients who provide the basis for this report, there were 73 men with a mean age of 68 years and 76 women with a mean age of 67 years. The mean blood pressure for the entire patient group was 158 mm Hg systolic and 81 mm Hg diastolic. Of the 149 patients, 141 (95%) were taking 1 or more antihypertensive medications, with 107 (72%) taking 2 or more, 49 (33%) taking 3 or more, and 15 (10%) taking 4 or more. With regard to specific types of antihypertensive medications, diuretics were being used by 79 (53%) of the patients, ß-blocking agents by 49 (33%), angiotensin-converting enzyme inhibitors by 54 (36%), and calcium channel blockers by 88 (59%). The clinical characteristics of the patient population at the baseline visit were as follows: 22 (15%) had a history of myocardial infarction, 48 (32%) had intermittent claudication, 13 (9%) had undergone a carotid endarterectomy, 19 (13%) had diabetes mellitus, and 124 (83%) were current or former cigarette smokers with a whole-group mean of 32 pack-years.

Table 2 lists the general factors, renal function parameters, and serum lipid levels for each of the ordered renal artery disease classes. Based on the Spearman correlation, the association between most of the features listed in Table 2 and the renal artery disease classes was weak. However, a positive correlation with p values in the range of 0.3 was noted for total cholesterol, LDL-C, and Apo B levels.

The distribution of renal, carotid, and lower extremity arterial disease in the 149 patients is shown in Table 3. Severe renal artery disease was present in 65 (44%) of the patients, compared with 29 (19%) with severe carotid artery disease and 32 (21%) with severe lower
extremity arterial disease. This higher proportion of patients with severe renal artery involvement reflects the patient selection process that was based solely on the presence of renal artery disease. There was a higher prevalence of moderate disease in the lower extremities compared with the carotid arteries, even though there was a similar prevalence of severe disease at both these sites.

The association between renal artery disease and carotid or lower extremity arterial disease is shown in Table 4 and Table 5. There was a weak trend for patients with increasing degrees of renal artery disease to also have increasing degrees of carotid and lower extremity arterial disease. The association of the ordered 3-level classification of renal artery involvement with the ordered 3-level classification for the other 2 arterial sites was not statistically significant (Spearman correlation for severity of renal and carotid arterial disease, $r=0.14, P=1$; the same values occurred for the correlation of renal and lower extremity arterial disease). The severity of carotid and lower extremity arterial disease was slightly more correlated in this population, with $r=0.23$ and $P=.006$.

From a clinical point of view, patients with either moderate or severe degrees of carotid or lower extremity arterial disease are of particular interest since they may require intervention or regular follow-up for disease progression. Further analyses were carried out to focus on these patient groups. Table 4 shows that the prevalence of severe carotid artery disease increases 4-fold as the degree of renal artery disease increases—from 7% in the mild renal artery group to 28% in the severe renal artery group. The severe renal artery group is about half again as likely to have moderate or severe lower extremity arterial disease than the mild renal artery group—66% vs 42% (Table 5). Overall, the proportion of patients in the moderate or severe disease groups was 48% for the carotid arteries and 59% for the lower extremity arteries.

The use of various clinical factors to predict the presence of severe renal, carotid, or lower extremity arterial involvement was investigated. This analysis concentrated on severe disease as a condition that is likely to require intervention. The Figure shows the odds ratio for severe disease compared with the combination of mild and moderate disease for each of the 3 arterial sites and for each of the clinical factors evaluated. For those factors that are not naturally dichotomous, the odds ratio represents risk for those above the median value...
compared with those below. The median value for each factor is also shown in the Figure. Statistically significant (P ≤ .05) or marginally significant (P ≤ .1) elevations in the odds ratio of severe disease for at least one of the renal, carotid, or lower extremity arterial sites were found for heavier cigarette smoking, increased systolic blood pressure or pulse pressure, abnormal renal function as reflected by high SUN or creatinine levels, elevated serum lipid levels (total cholesterol, LDL-C, total triglycerides, ApoB), and severe renal artery disease. The most

### Table 1. Definitions of Mild, Moderate, and Severe Disease for the Renal, Carotid, and Lower Extremity Arteries*

<table>
<thead>
<tr>
<th>Disease</th>
<th>Renal Duplex</th>
<th>Carotid Duplex</th>
<th>Lower Extremity ABI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Normal or &lt;60% bilaterally†</td>
<td>Normal or 16%-49% bilaterally</td>
<td>≥0.95 Bilaterally</td>
</tr>
<tr>
<td>Moderate</td>
<td>≥60% Contralateral to &lt; 60% or normal</td>
<td>50%-79% Contralateral to 50% -79% or less; or occluded contralateral to not occluded</td>
<td>0.50-0.94 Contralateral to ≥0.95</td>
</tr>
<tr>
<td>Severe</td>
<td>≥60% Bilaterally; or occluded contralateral to not occluded</td>
<td>80%-99% Contralateral to 80%-99% or less; or occluded contralateral to not occluded</td>
<td>&lt;0.50 on either leg</td>
</tr>
</tbody>
</table>

*Classification accounts for the extent of disease on both sides. ABI indicates ankle/brachial index.
†Eligibility for patient recruitment requires at least 1 abnormal renal artery, thus there are no patients with normal renal arteries bilaterally.

### Table 2. Association of General Factors, Renal Function Parameters, and Serum Lipid Levels With Renal Artery Disease Classes*

<table>
<thead>
<tr>
<th>General factors</th>
<th>Overall</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Spearman Correlation (r)† PMild Moderate Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 149</td>
<td>n = 29</td>
<td>n = 55</td>
<td>n = 65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>68 ± 9</td>
<td>67 ± 10</td>
<td>68 ± 9</td>
<td>67 ± 9</td>
<td>−0.01 .9</td>
</tr>
<tr>
<td>% Female</td>
<td>51</td>
<td>55</td>
<td>51</td>
<td>49</td>
<td>† .9</td>
</tr>
<tr>
<td>% With diabetes mellitus</td>
<td>13</td>
<td>14</td>
<td>15</td>
<td>12</td>
<td>† .9</td>
</tr>
<tr>
<td>Smoking, pack-years</td>
<td>32 ± 30</td>
<td>34 ± 30</td>
<td>31 ± 32</td>
<td>31 ± 29</td>
<td>−0.01 .9</td>
</tr>
<tr>
<td>Systolic BP , mm Hg</td>
<td>158 ± 25</td>
<td>148 ± 19</td>
<td>161 ± 28</td>
<td>159 ± 24</td>
<td>0.11 .2</td>
</tr>
<tr>
<td>Diastolic BP , mm Hg</td>
<td>81 ± 10</td>
<td>77 ± 9</td>
<td>83 ± 11</td>
<td>80 ± 10</td>
<td>0.05 .6</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>77 ± 23</td>
<td>71 ± 20</td>
<td>79 ± 25</td>
<td>79 ± 21</td>
<td>0.10 .2</td>
</tr>
</tbody>
</table>

### Table 3. Distribution of Renal, Carotid, and Lower Extremity Arterial Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Renal Arteries</th>
<th>Carotid Arteries</th>
<th>Lower Extremities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>29 (19)</td>
<td>77 (52)</td>
<td>61 (41)</td>
</tr>
<tr>
<td>Moderate</td>
<td>55 (37)</td>
<td>43 (29)</td>
<td>56 (38)</td>
</tr>
<tr>
<td>Severe</td>
<td>65 (44)</td>
<td>29 (19)</td>
<td>32 (21)</td>
</tr>
</tbody>
</table>

*See Table 1 for a description of disease severity.

### Table 4. Association Between Renal and Carotid Artery Disease*

<table>
<thead>
<tr>
<th>Renal Artery Disease</th>
<th>No. of Patients</th>
<th>Carotid Artery Disease, %</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>29</td>
<td>59</td>
<td>35</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>55</td>
<td>53</td>
<td>31</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>65</td>
<td>48</td>
<td>25</td>
<td>28</td>
<td></td>
</tr>
</tbody>
</table>

*Spearman correlation between renal and carotid arterial disease classes, 0.14 (P = .1).

### Table 5. Association Between Renal and Lower Extremity Artery Disease*

<table>
<thead>
<tr>
<th>Renal Artery Disease</th>
<th>No. of Patients</th>
<th>Lower Extremity Arterial Disease, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>29</td>
<td>59 (21)</td>
</tr>
<tr>
<td>Moderate</td>
<td>55</td>
<td>40 (20)</td>
</tr>
<tr>
<td>Severe</td>
<td>65</td>
<td>43 (23)</td>
</tr>
</tbody>
</table>

*Spearman correlation between renal and lower extremity arterial disease classes, 0.14 (P = .1).
predictive factors for each site were elevated Apo B (renal artery) levels, high SUN (carotid artery) levels, and smoking (lower extremity arteries), all having odds ratios of approximately 3.0 or more for high vs low levels. The presence of severe renal artery disease was predictive of severe carotid artery disease but not of severe lower extremity arterial disease.

Various combinations of the dichotomous factors in the Figure were also tested to evaluate whether they could help predict the presence of severe arterial disease. This analysis suggested that either SUN or creatinine levels can be useful in predicting severe carotid artery disease among patients with renal artery stenosis; however, the other factors provide little additional predictive value when SUN or creatinine values are known. For the lower extremity, the combination of smoking, increased pulse pressure, and elevated total triglyceride levels is predictive of severe disease, and the remaining factors in the Figure do not add to the predictive value of this combination. The degree of renal artery disease is of little importance in predicting the presence of severe carotid or lower extremity arterial disease when these other factors are known.

The coexistence of atherosclerotic lesions in the renal, carotid, and lower extremity arteries has been documented previously. In a series of 395 consecutive patients undergoing arteriography, a renal artery stenosis of 50% or more was found in 38% of patients with abdominal aortic aneurysms, 33% of patients with aortoiliac occlusive disease, and 39% of patients with lower extremity arterial disease.17 In a case-control study of patients with renovascular or primary hypertension, carotid artery lesions were found by duplex scanning in 83% and 43%, respectively.18

An earlier review of 60 patients in the renal artery natural history study who also had carotid artery duplex scans and ABI measurements was reported in 1994.11 A high-grade internal carotid artery stenosis (≥50% diameter reduction) or occlusion was found in 46% of the patients with at least 1 renal artery lesion with a diameter reduction that was 60% or greater, but in only 25% of those with lesser degrees of renal artery disease. An abnormal ABI (<0.95) was present in 73% of the patients with renal artery lesions with a diameter reduction of 60% or higher compared with 50% of the patients with renal artery lesions with a diameter reduction that was less than 60%. The present study is an extension of this initial report which now includes a larger patient population and accounts for the severity of disease on both sides for all 3 arterial sites. In addition, the present study provides an analysis of atherosclerotic risk factors and other clinical parameters for renal, carotid, and lower extremity arterial disease.

It should be emphasized that the association between renal, carotid, and lower extremity arterial disease in the present study is based on observations made at a single point in time. Therefore, no definite conclusions can be made regarding the causation of disease at
these 3 arterial sites. There was an overall trend for patients to have increasing degrees of carotid and lower extremity arterial disease in association with increasing degrees of renal artery disease. This was particularly apparent in the carotid artery, with the frequency of severe carotid artery disease increasing from 7% in the mild renal artery group to 28% in the severe renal artery group (Table 4). Thus, severe renal artery disease can be considered predictive of severe carotid artery disease. Various clinical factors may also be useful in predicting the presence of severe disease in the renal, carotid, and lower extremity arteries. In this study population, the most predictive single factors were elevated Apo B levels for the renal arteries, high SUN levels for the carotid arteries, and smoking for the lower extremity arteries. A combination of risk factors—smoking, increased pulse pressure, and elevated total triglyceride levels—provided additional predictive value only for lower extremity arterial disease.

The biological rationale for the associations observed in this study is a matter for speculation. For example, the association between diminished renal function and severe carotid disease could be related to the tendency for patients with severe renal artery disease to also have severe carotid artery disease. The diminished renal function in these patients would be a consequence of renal artery stenosis. Other associations, such as those between increased systolic blood pressure and severe carotid artery disease, or heavier cigarette smoking and severe lower extremity arterial disease, are not unique to this study. Hypertension is recognized as one of the most prevalent and significant risk factors for cardiovascular disease, and isolated systolic hypertension is the predominant variety. The prevalence of isolated systolic hypertension increases with age. Elevated blood pressure is one of several factors that have been associated with increasing degrees of extracranial carotid artery atherosclerosis. Data from the Framingham study indicate that isolated systolic hypertension predisposes to stroke; however, the diastolic component contributes relatively little to the overall risk assessment. Cigarette smoking is also a major determinant of cardiovascular morbidity and mortality that is independent of blood pressure levels. There is a particularly strong relationship between the severity of peripheral arterial disease and cigarette smoking.

Historically, the surgical management of renovascular disease initially focused on patients with hypertension and localized renal artery atherosclerosis or fibromuscular dysplasia. Percutaneous transluminal balloon angioplasty has been effective in treating fibromuscular dysplasia of the main renal artery, but the long-term results with atherosclerotic lesions have been inconsistent. During the last decade, an increasing proportion of patients requiring renal revascularization has presented with advanced widespread atherosclerosis and renal insufficiency. This trend may be due, at least in part, to improved pharmacological treatment of hypertension and cardiovascular disease in general. Thus, the patients currently being considered for renal artery interventions tend to have significant medical comorbidity and often require complex vascular reconstructions or bilateral renal artery procedures.

With regard to lower extremity arterial occlusive disease, direct intervention is only mandatory when there is critical ischemia and threat of limb loss. This typically occurs with multiple-level disease and is associated with ABI values of 0.5 or less. A decreased ABI may also be useful as a clinical indicator of risk for myocardial infarction, stroke, or transient ischemic attack. Patients with renal artery disease and signs or symptoms of peripheral ischemia should be screened for lower extremity arterial occlusive disease with ABI measurements. Further decisions can then be made concerning the need for more definitive diagnostic tests and intervention.

The therapeutic approach to carotid artery disease is somewhat different because carotid endarterectomy is indicated in selected patients with asymptomatic carotid stenoses of 60% or greater diameter reduction. Based on the association observed in this study between the finding of renal artery and carotid artery disease, noninvasive carotid artery screening appears to be justified in patients with renal artery lesions. The combined prevalence of moderate and severe carotid artery disease in the study population ranged from 42% for patients with mild renal artery disease to 53% for those with severe renal artery disease. When a severe carotid artery stenosis is found, the patient should be considered for operation. If less severe carotid artery disease is present, follow-up by serial duplex scanning may be warranted to detect disease progression. The development of hemispheric neurologic symptoms should also prompt a noninvasive evaluation of the carotid arteries, since endarterectomy is indicated for symptomatic carotid artery stenosis with a 70% or higher diameter reduction. An aggressive policy of screening, follow-up, and intervention for carotid artery disease might facilitate stroke prevention in patients with renal artery atherosclerosis.

In summary, this cross-sectional study of 149 patients with renal artery atherosclerosis indicates that there is an association between the degree of renal artery disease and the degree of disease in the extracranial carotid and lower extremity arteries. This analysis also identified predictive factors for severe disease at each of the 3 arterial sites. Single factors are helpful in predicting the presence of severe disease in the carotid (SUN or creatinine levels) and renal (Apo B levels) arteries. In the lower extremity arteries, a combination of risk factors (smoking, pulse pressure, and total triglyceride levels) is associated with severe disease. While lower extremity atherosclerosis is relatively common in this patient population, noninvasive screening can generally be reserved for patients with signs or symptoms of peripheral ischemia. However, noninvasive carotid artery screening is justified in patients with renal artery disease to detect asymptomatic lesions that may require surgical treatment or serial follow-up. A goal of this ongoing study is to document disease progression in the renal, carotid, and lower extremity arteries over time. Future analyses will address the rates and risk factors for disease progression at these 3 arterial sites.
REFERENCES


