Renal Resistance Index and Progression of Renal Disease

Jörg Radermacher, Sebastian Ellis, Hermann Haller

Abstract—The progression of renal disease depends on various clinical parameters such as hypertension and proteinuria. We recently showed that an increased renal resistance index measured by duplex ultrasound is associated with a poor prognosis in patients with renal artery stenosis. We now prospectively tested the hypothesis that a high renal resistance index (≥80) predicts progression of renal disease in patients without renal artery stenosis. In 162 patients newly diagnosed with renal disease, the resistance index (1-[end diastolic velocity/maximum systolic velocity]*100) was measured in segmental arteries of both kidneys. Creatinine clearance was measured at baseline, at 3, 6, and 12 months, and then at yearly intervals thereafter (mean follow-up 3±1.4 years). The combined endpoint was a decrease of creatinine clearance by ≥50%, end-stage renal disease with replacement therapy, or death. Twenty-five patients (15%) had a renal resistance index value ≥80 at baseline. Nineteen (76%) had a decline in renal function; 16 (64%) progressed to dialysis, and 6 (24%) died. In comparison, in patients with renal resistance index values <80, 13 (9%) had a decline in renal function, only 7 (5%) became dialysis-dependent, and 2 (1%) died (P<0.001). In a multivariate regression analysis, only proteinuria and resistance index were independent predictors of declining renal function. A renal resistance index value of ≥80 reliably identifies patients at risk for progressive renal disease. (Hypertension. 2002; 39[part 2]:699-703.)

Key Words: ultrasonography ■ vascular resistance ■ renal disease ■ risk factors

Chronic renal disease may be characterized by a progressive loss of renal function resulting in end-stage renal failure; however, the rate of decline is highly variable. Predicting future decline in renal function is important for subsequent therapeutic decisions. Risk factors for a more rapid decline include hypertension proteinuria and hypercholesterolemia, as well as severity of impairment at the time of diagnosis, male gender, and age.1–3 Progressive chronic renal disease probably reflects a nonspecific renal scarring process characterized by interstitial fibrosis, loss of capillaries and glomeruli, resulting in a reduction in the number and area of renal vessels.4,5 This reduction may in turn be responsible for increased intrarenal vascular resistance. Assessment of intrarenal vascular resistance may therefore be helpful in determining the degree of intrarenal damage and may be useful in predicting the subsequent function of the diseased kidney. Increased renal resistance can be measured by Doppler ultrasonography. We showed earlier that an increased renal resistance index value >80 is a strong predictor of renal functional decline in patients with renal artery stenosis, despite correction of the stenosis.6 We therefore hypothesized that in patients with chronic renal disease of any cause, an increased renal resistance index may correlate with the rate of decline in renal function and predict the course of the disease.

Methods
Between June 1995 and September 1999, we performed color Doppler ultrasonography on 162 consecutive patients with renal disease who were referred to, and afterward regularly visited, our outpatient department. All patients had one or more of the following: creatinine clearance <75% of the normal value for age and gender, proteinuria >150 mg/d, diabetes mellitus and/or hypertension, or other established chronic renal disease. Patients with renal artery stenosis were excluded from further analysis. The patients were divided according to their segmental artery resistance index values in a group with values of ≥80 and a group with values <80.

The methods for exclusion of renal artery stenosis with color Doppler ultrasonography and for measuring renal segmental artery resistance index have been published previously.6,7 Briefly, resistance index was measured with an Ultramark 9 HDI ultrasound machine (Advanced Technology Laboratories) using either a C2 to 4 MHz-curved array or a P 2 to 3 sector multifrequency transducer with a 2.5 MHz pulsed Doppler frequency and a focal zone at the depth of the renal arteries. Peak systolic velocity (Vmax [cm/sec]) and end diastolic velocity (Vmin [cm/sec]) were obtained for the calculation of the dimensionless resistance index values: resistance index=100×(1−[Vmin/Vmax]). Resistance index was calculated as the average of 4 to 6 measurements in segmental arteries from the upper, middle, and lower third of both kidneys. The Doppler angle was chosen as close to 0° as possible and special care was taken not to compress the kidney and not to have the patient perform a Valsalva maneuver because both can increase the renal resistance index value. In addition, the renal volume (in cm³) was estimated in all patients as renal length (cm) × renal width (cm) × renal depth (cm)/2. The normal renal volume was calculated as 2 × body weight (kg), according to findings by Rasmussen8 and our own data in 100 healthy kidney donors (unpublished data). The ultrasound studies with measurement of resistance index and renal volume were approved by the institutional ethics committee of the Hannover Medical School. All patients gave written informed consent.

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699
Blood pressure (24-hour ambulatory blood pressure Monitor 90217, Spacelab) and creatinine clearance (ml/min per 1.73 m²) were measured at baseline and erythrocyte sedimentation rate; 24-hour urinary protein excretion, serum-cholesterol, and serum uric acid were determined by standard laboratory methods. After the initial presentation, patients were seen at 3 months, 6 months, 12 months, and at yearly intervals thereafter for determination of creatinine clearance and 24-hour urinary protein excretion and for adjustment of blood pressure. The combined endpoint of the study was a decrease in creatinine clearance of at least 50%, end-stage renal disease necessitating replacement therapy, or death of the patient at the last available follow-up. Dialysis status and death were ascertained by contact with the patients or their relatives. The average duration of follow-up was 3.0 ± 1.4 years (range 1.0 to 5.1 years).

The ultrasound study did not involve any form of active treatment and is consistent with the principles of the Declaration of Helsinki. Statistical software programs (SPSS, version 10.0.7, SPSS Inc, and SAS, version 8.0, SAS Institute) were used. Unpaired t tests with Bonferroni adjustment for multiple tests at different time points or χ² square analysis were used as appropriate to assess differences between groups. Odds ratios for worsening of renal function for various risk factors were calculated from 2-by-2 contingency tables (Fisher’s exact test). For multivariate analysis, the effects of resistance index, mean ambulatory 24-hour systolic and diastolic blood pressure, pulse pressure, nocturnal decrease in blood pressure, antihypertensive drugs (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-adrenergic receptor blockers, diuretics, clonidine, alpha-receptor blockers, hydralazine, moxonidine, minoxidil), age, gender, body mass index, kidney volume, presence of atherosclerosis in the heart, legs or central nervous system, diabetes mellitus, smoking use, years since onset of hypertension, left ventricular hypertrophy, and proteinuria on the combined endpoint were analyzed in all 162 patients with stepwise forward logistic regression (significance level for removing the variable from analysis = 0.1, for entering the variable = 0.05). All data are expressed as means ± SD.

### Results

Table 1 shows the initial demographic characteristics distinguishing the 25 patients with renal resistance index ≥80 from the 137 patients with an index <80. The patients with high resistance index were older, sicker, smoked more, were more likely to be diabetic, had higher systolic and pulse pressures, took more antihypertensive drugs, excreted more protein, had lower creatinine clearances, and a higher erythrocyte sedimentation rate, compared with those with low resistance index. Patients with resistance index ≥80 took more ACE-inhibitors (64% versus 36%), more calcium channel blockers (76% versus 35%), diuretics (76% versus 38%), clonidine (24% versus 3%), and more nitrates (32% versus 8%). Over time, the 25 patients whose resistance index values were ≥80 had decreases in renal function, became dialysis-dependent, or died (Figure 1A) compared with patients with resistance index <80 who remained generally stable. These differences persisted after matching for creatinine clearance (Figure 1B) and proteinuria (Figure 1C). Patients with resistance index ≥80 had a mean renal survival rate after 1 year of 43%, compared with 99% in patients with resistance index values <80. The renal resistance index value was correlated with the change in creatinine clearance (Figure 2).

Table 2 shows the sensitivity, specificity, positive and negative predictive values of the renal resistance index, proteinuria >1 g/d, creatinine clearance <40 mL/min, and elevated ESR. The renal resistance index was a specific prognostic indicator with a high positive and negative predictive value. Of the seven patients who became dialysis dependent and died between 1993 and 2000, six had resistance index values ≥80. The seventh patient, who had a resistance index value of 80.4, was a 68-year-old black man with hypertension, left ventricular hypertrophy, diabetes mellitus, and elevated creatinine clearance who died of a myocardial infarction. All of these patients had high proteinuria, creatinine clearance <30 mL/min, and elevated ESR. The renal resistance index was a strong independent predictor of renal survival and death in this population. It was comparable to the glomerular filtration rate, serum creatinine, and proteinuria in its capacity to predict renal survival in this population.

### Table 1. Demographic Characteristics Distinguishing Renal Resistance Index ≥80 Patients From Patients With Lower Renal Resistance Indices (mean±SD)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>≥80</th>
<th>&lt;80</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>25</td>
<td>137</td>
<td>...</td>
</tr>
<tr>
<td>Age</td>
<td>66±10</td>
<td>47±16</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.6±4.2</td>
<td>25.7±4.5</td>
<td>0.04</td>
</tr>
<tr>
<td>Documented atherosclerosis, n (%)</td>
<td>15 (60)</td>
<td>25 (18)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Coronary disease, n (%)</td>
<td>13 (52)</td>
<td>18 (13)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peripheral arterial disease, n (%)</td>
<td>10 (40)</td>
<td>9 (7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>10 (40)</td>
<td>11 (8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cigarettes total pack, y</td>
<td>34±12</td>
<td>20±12</td>
<td>0.005</td>
</tr>
<tr>
<td>ABPM 24-h systolic pressure, mm Hg</td>
<td>160±23</td>
<td>144±22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ABPM pulse pressure, mm Hg</td>
<td>75±23</td>
<td>56±15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension duration, y</td>
<td>15±11</td>
<td>7±10</td>
<td>0.001</td>
</tr>
<tr>
<td>Antihypertensive drug classes</td>
<td>3.3±1.7</td>
<td>1.8±1.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>69±11</td>
<td>68±11</td>
<td>0.52</td>
</tr>
<tr>
<td>Uric acid, mg/dL</td>
<td>7.1±2.3</td>
<td>5.8±1.8</td>
<td>0.003</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min/1.73 m²</td>
<td>24±16</td>
<td>91±31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Protein excretion, g/d</td>
<td>2.6±2.2</td>
<td>0.5±1.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate, mm²/h</td>
<td>42±22</td>
<td>13±12</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

ABPM denotes 24-hour ambulatory blood pressure measurements; diastolic blood pressures were not different. Antihypertensive drug classes: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-adrenergic receptor blockers, diuretics, clonidine, alpha-receptor blockers, hydralazine, moxonidine, minoxidil. To convert the values for serum uric acid to micromoles per liter, multiply by 59.5.

P values according to unpaired t test or χ² test.
dependent but had resistance index values below 80, two had polycystic kidney disease, and four had chronic glomerulonephritis, diseases that are known to deteriorate more quickly.9 In a univariate analysis (Figure 3), only impaired creatinine clearance and elevated creatinine concentrations had a predictive value as strong as the resistance index value, as shown by the odds ratios for prediction of worsening renal function. Table 3 shows the results of univariate and multivariate analyses with calculated odds ratios for worsening renal function, dialysis, or death. In the multivariate analysis, the renal resistance index was superior in indicating odds ratios for worsening renal function or death, compared with proteinuria >1 g/d or creatinine clearance <40 mL/min. Only the renal resistance index and proteinuria >1 g/d were independent variables indicating progression. The same findings were obtained after correction of resistance index values for a pulse rate of 70 according to the formula of Schwerk and Restrepo.10 Of the 137 patients with renal resistance index values ≥80, 2 died, 7 required dialysis, and 13 (9%) developed a deterioration in renal function ≥50%. In contrast, among the 25 patients who had resistance index values <80 at baseline, 6 (24%) died during follow-up, 16 (64%) became dialysis-dependent, and renal function worsened in 19 (76%) (all P<0.001).

Discussion

The important finding in this study was that the renal resistance index ≥80 proved to be a strong, independent predictor of renal disease progression. The resistance index can be easily obtained noninvasively, in the process of ruling out renal vascular hypertension for example, and thereby promises to become a worthwhile tool in the diagnostic armamentarium. Admittedly, our patients with high resistance index values were sicker than patients with lower values and other indicators such as proteinuria and low

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### TABLE 2. Sensitivity, Specificity, Positive and Negative Predictive Value to Predict Deterioration in Renal Function* or Death of the Patient

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance index &gt;80 and deterioration of renal function or death, %</td>
<td>64 (23/36)</td>
<td>98 (124/126)</td>
<td>92 (23/25)</td>
<td>91 (124/137)</td>
</tr>
<tr>
<td>Proteinuria &gt;1 g/day and deterioration of renal function or death, %†</td>
<td>88 (30/34)</td>
<td>91 (113/124)</td>
<td>73 (30/41)</td>
<td>97 (113/117)</td>
</tr>
<tr>
<td>Creatinine clearance &lt;40 ml/min and deterioration of renal function or death, %</td>
<td>83 (30/36)</td>
<td>96 (121/126)</td>
<td>86 (30/35)</td>
<td>95 (121/127)</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate &gt;30 mm/h and deterioration of renal function or death, %</td>
<td>62 (21/34)</td>
<td>90 (113/125)</td>
<td>64 (21/33)</td>
<td>90 (113/126)</td>
</tr>
</tbody>
</table>

Numbers in parentheses are numbers of patients.

*Decrease of the creatinine clearance by at least 50% or dialysis dependence.
†Data on proteinuria are missing in 4 patients.
creatinine clearance were also important indicators of disease progression. However, in terms of positive and negative prediction, the renal resistance index demonstrated superior utility. The differences in resistance index values between the two groups were not secondary to pulse rate or use of antihypertensive medications because pulse rates did not differ and because twice as many antihypertensive drugs, which were expected to lower resistance index values, were used in the group with high resistance index values. Our data are supported by findings in African-American patients, who, at the same level of hypertension, have higher renal vascular resistance and are more prone to develop end stage renal disease than white patients.

Progressive chronic renal failure is believed to reflect a nonspecific renal scarring process involving all renal components. The process results in a reduction in the number and area of postglomerular capillaries. Renal scarring ultimately leads to a reduction in the intrarenal vessel area, which in turn may be responsible for an increased intrarenal vascular resistance. Assessment of intrarenal vascular resistance may therefore be helpful in determining the degree of intrarenal damage. How much the three different renal vascular beds, preglomerular vessels, glomerular capillaries, and postglomerular vessels contribute to the raised resistance index is unclear. Studies in patients with diabetic nephropathy suggested that the postglomerular vessels were the major contributor to increased resistance, although glomerulosclerosis and not interstitial fibrosis is the histological hallmark of this disease.

Patients with essential hypertension have a higher renal vascular resistance, even without overt nephropathy, and uniformly show decreased renal perfusion. In hypertensive patients glomerular filtration rate is generally maintained, also suggesting a more pronounced vasoconstriction or scarring distal to the glomerulus. Nevertheless, the pathognomonic histological sign of hypertensive nephropathy is preglomerular arteriolar hyalinosis. In cholesterol embolism, a relatively common disease in the elderly, the arterial bed proximal to the glomerulus is the site of injury. Aside from this condition, the alteration in renal vascular resistance is probably functional and reversible in early renal insufficiency and structural and irreversible in advanced renal disease.

Various risk factors identify patients at increased risk of worsening renal function. The three most accepted parameters are proteinuria, severely impaired renal function at initial presentation, and hypertension. Proteinuria and impaired baseline renal function were good prognostic indicators in our study also. However, neither systolic nor diastolic blood pressure at initial presentation significantly influenced the outcome. This finding is not surprising because patients with hypertensive nephrosclerosis frequently maintain stable function over long periods once their blood pressure has been brought under control. Good blood pressure control was a primary goal in our outpatient clinic. Pulse pressure remained a risk factor for deterioration of renal function or death. Lowering pulse pressure remains extremely difficult with currently available drugs.

We also found that the erythrocyte sedimentation rate (ESR), a missing nocturnal decrease in blood pressure (dipping), advanced age, hyperuricemia, duration of hypertension, atherosclerosis, diabetes mellitus, and increased pulse pressure were associated with the rate of decreasing renal function. Interestingly, the ESR had fairly good prognostic value regarding worsening renal function. ESR may reflect general inflammation, similar to increased C-reactive protein, a cardiovascular risk factor not measured in our study. We are currently available drugs. However, the ESR is also increased in patients with heavy proteinuria. Proteinuria was greater in patients with deteriorating renal function. Therefore, we cannot be certain whether ESR is directly related to worsening renal function or death, or indirectly via increased proteinuria.

It is unclear at present whether an increased renal resistance index value indicates irreversible renal scarring or whether there are strategies that could favorably influence the renal resistance value and thereby improve the prognosis of the patient. Because these patients have a particularly unfa-
favorable prognosis, aggressive strategies to preserve the renal vasculature are sorely needed.

Acknowledgments
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References


