Epidemiology of Renal Dysfunction and Patient Outcome in Atherosclerotic Renal Artery Occlusion

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Abstract. Patients with atherosclerotic renal artery occlusion (RAO) effectively have only a single functioning kidney, so they constitute an ideal group in whom to study the relationship of atherosclerotic renovascular disease (ARVD) severity to renal functional outcome. Of 299 patients with ARVD who had presented to a single center over a 12-yr period, 142 (47.5%) patients with RAO were identified. There was no relationship between baseline renal function and contralateral renovascular anatomy. Patients with contralateral normal, insignificant (<50%), or significant (>50%) renal artery stenoses had baseline creatinine of 243 ± 235, 292 ± 197, or 210 ± 102 μmol/L, respectively, but patients with bilateral RAO (creatinine, 540 ± 304 μmol/L; P < 0.0001) were significantly worse. There were significant correlations between baseline GFR and both proteinuria (r = −0.32; P < 0.01) and contralateral bipolar renal length (r = 0.44; P < 0.0001). Over a mean follow-up period of 31 ± 21 (2 to 82) mo, the overall rate of progressive renal functional decline was −4.1 ml/min per yr. Nine patients required dialysis at presentation and a further 15 (10.5%) during the course of the study. There were 85 (59.9%) deaths; median survival of the whole group was 25 mo, and 5-yr survival was 31%. Multivariate analysis indicated that low baseline GFR was the chief variable independently associated with increased probability of death or need of dialysis but that renal vascular anatomy had no prognostic impact. This study reinforces the importance of intrarenal vascular and parenchymal disease in the etiology of renal dysfunction in ARVD.

Atherosclerotic renovascular disease (ARVD) is common, and it is associated with chronic renal failure in many patients (1). It is well recognized that this renal impairment can be progressive and that large numbers of patients with ARVD are now reaching end-stage renal failure (ESRF) and entering renal replacement therapy (RRT) programs (2). These patients have a high mortality because of associated extrarenal vascular disease. However, despite the high prevalence of these patients, the pathogenesis of the renal dysfunction that occurs in association with ARVD is still not fully understood.

Early studies demonstrated a relatively rapid rate of progression of high-grade renal artery stenosis (RAS) to renal arterial occlusion (RAO) with consequent loss of functioning renal mass (3,4), and this, coupled with the increasing burden of patients with ARVD developing ESRF, has underpinned the rationale to maintain renal arterial patency by revascularization procedures. However, evidence now suggests that progressive renal arterial narrowing and renal ischemia are likely to cause renal impairment in only a minority of patients with ARVD. Other factors, such as coexisting hypertensive and atherosclerotic damage to the renal parenchyma (5,6), may be more often important in the pathogenesis of renal failure. For example, the effects of revascularization on renal functional outcome are unpredictable, and this is true irrespective of the nature of the revascularization technique. Hence, after angioplasty, with or without stenting, or surgery, the majority of patients with severe RAS lesions manifest no improvement in renal function, and some show a progressive renal functional decline despite restoration of renal artery patency (7–11). Furthermore, patients with nonsignificant RAS lesions (<50% to 60%) may progress to ESRF, and we have recently shown that no overall correlation exists between proximal renal arterial disease severity and renal failure in patients with ARVD (12). Isotopic studies that estimate single-kidney GFR (SK-GFR) have shown that renal dysfunction can be just as severe in the contralateral kidney that has a normal renal artery as in the kidney affected by the significant RAS lesion (13).

Most studies that have sought to define the outcome of patients with ARVD have included patients with heterogeneity of renovascular lesions, and few have specifically examined patients with RAO. Patients with RAO are likely to have extensive coexisting extrarenal vascular disease (14), and their rate of mortality may be even higher than in those patients with ARVD with lesser lesions (15). Because these patients effectively have only a single functioning kidney, their baseline level of renal dysfunction as well as renal functional outcome should theoretically be attributable to changes in the kidney contralateral to the RAO. We studied a large number of patients with atherosclerotic RAO with the aims of further clar-
ifying the pathogenesis of renal impairment in patients with ARVD and of describing the renal functional and mortality outcomes of this high-risk subgroup of patients with ARVD.

Materials and Methods

Patient Selection

The Hope Hospital ARVD database has captured data on all patients referred to this hospital (catchment population 1.1 million for renal referrals) with ARVD between 1987 and the present day; data have been collected prospectively since 1995. The population for the current study consisted of all those patients on the database who were confirmed to have either unilateral or bilateral RAO that was characteristic of atherosclerotic disease; two patients with RAO associated with fibromuscular hyperplasia were excluded. All patients had been referred with acute or chronic renal failure, hypertension, or a combination of these clinical features.

Renal Angiography

Renal arterial anatomy was investigated by digital subtraction angiography, the studies being interpreted by a single vascular radiologist who was unaware of the clinical data. The digital subtraction angiography protocol involved two 50-ml contrast runs. During the first run, the screening of the renal areas was extended to 60 s to delineate the nephrograms. RAO was confirmed by the presence of a proximal renal artery stump, usually coupled with either an absent or slightly delayed nephrogram; these findings were verified during the second contrast run. The percentage stenosis of any RAS in the contralateral kidney was estimated by standard methodology; the reference diameter was the renal artery luminal diameter immediately distal to the stenosis (except in cases with poststenotic dilatation, in which case the diameter immediately distal to the dilated segment was used):

\[
\text{Contralateral renal stenosis} = \left( \frac{\text{reference diameter} - \text{narrowest diameter}}{\text{reference diameter}} \right) \times 100\% 
\]

Contralateral renal arterial anatomy was then classified as normal, insignificant RAS (any detectable stenosis <50%), significant RAS (stenosis >50%), or RAO. For the purposes of further analysis, the severity of contralateral disease was also described according to residual proximal renal artery luminal patency (e.g., normal, 1.0; 75% RAS, 0.25; and RAO, 0), a descriptive technique that has been used elsewhere (12).

Investigative Methods

An analysis of all those patients found to have atherosclerotic RAO between 1987 and 1999 was undertaken; this was retrospective for patients who presented before 1995 and prospective for the patients treated after that date. Basic patient demography and subsequent clinical data were recorded. The baseline patient characteristics at the time of angiographic diagnosis included age, gender, weight, BP, and the presence of extrarenal vascular disease, which was defined as a clinical history or angiographic evidence of angina or myocardial infarction or cerebrovascular or peripheral vascular disease. Other baseline information included creatinine, 24-h urinary protein excretion, and bipolar renal length as determined by renal ultrasound. In patients with bilateral RAO, contralateral renal size was taken as the average of the two kidney lengths for each patient.

GFR was estimated by use of the Cockcroft and Gault formula (16); creatinine and estimated GFR were measured both at baseline and at the latest follow-up. For the purpose of further analysis, patients were grouped according to their baseline level of renal dysfunction:

- Mild renal failure: estimated GFR, >50 ml/min;
- Moderate renal failure: estimated GFR, 25 to 50 ml/min;
- Severe renal failure: estimated GFR, 10 to 25 ml/min;
- ESRF: estimated GFR, <10 ml/min.

Renal functional outcome was assessed by the rate of change of GFR per year (ml/min per yr) of the follow-up period. A >20% decrease in GFR below the baseline value was considered to be a significant decline of renal function. The other major outcome variables studied were the time to requirement of RRT and survival.

Statistical Analyses

Parametric data are presented as mean ± SD. Variables were compared by use of ANOVA. Categorical data were compared by use of χ² tests. Correlation regression was used to test the relationships among GFR, renal size, severity of renovascular disease, and proteinuria. Survival analysis was used to study renal and/or patient survival. Proportional-hazards analysis was used to compare outcomes according to anatomic subgroup, with adjustment for baseline GFR.

Results

Patient Characteristics

During the period from 1987 to June 1999, there were 299 patients with angiographically proven ARVD. A total of 142 patients (47.5%) had evidence of RAO; 68 were men and 74 women (gender ratio, 1:1.1). Their mean age at the time of investigation was 66.1 ± 11.4 (range, 26.3 to 90.1) yr, with the men 65.5 ± 11.7 (range, 26.3 to 90.1) yr and women 66.5 ± 11.1 (range, 31.9 to 86.9) yr. Although baseline renal functional data were available in 138 patients (Table 1) and data regarding renal size and proteinuria in even fewer, death and dialysis outcomes were available for all patients. Incomplete data sets arose for several reasons, which included the patient dying during the early stages of their hospital stay (and before, e.g., proteinuria had been assessed), the patient having been discharged to consultant care at another hospital, or because the laboratory reports had been separated from the medical records. The latter was only a problem for patients who presented with ARVD before 1995, i.e., during the period for which data were collected retrospectively.

Hypertension (defined as systolic BP >160 mmHg and/or diastolic BP >90 mmHg (17) or controlled with antihypertensive medications) was evident in 90.2% of patients. Only 15 patients (10.5%) had diabetes mellitus (all had type II diabetes).

Contralateral Renovascular Disease Severity and Extrarenal Vascular Disease

Table 1 shows the clinical characteristics of the patients grouped according to the severity of contralateral renovascular disease at baseline; 80 (56.3%) patients had a normal contralateral vessel, 19 (13.4%) had insignificant (RAS <50%), and 26 (18.3%) had significant (RAS >50%) contralateral renovascular narrowing, and 17 (12.0%) had bilateral RAO. The prevalence of hypertension and use of antihypertensive drugs was similar within these subgroups. Overall, 92 patients (70%) had evidence of extrarenal vascular disease, with 43% having given
### Table 1. Contralateral renal artery anatomy

<table>
<thead>
<tr>
<th></th>
<th>Normal n = 80 (56.3%)</th>
<th>RAS &lt;50% n = 19 (13.4%)</th>
<th>RAS ≥50% n = 26 (18.3%)</th>
<th>RAO n = 17 (12.0%)</th>
<th>n = 142</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>No. studied</td>
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<td>19</td>
<td>26</td>
<td>16</td>
<td>138</td>
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<tr>
<td>mean baseline serum creatinine ± SD (range) [μmol/L]</td>
<td>242.6 ± 235.3 (69 to 1698)</td>
<td>291.6 ± 197.4 (87 to 789)</td>
<td>210.2 ± 102.1 (63 to 555)</td>
<td>539.6 ± 303.9 (189 to 1062)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. studied</td>
<td>72</td>
<td>19</td>
<td>25</td>
<td>15</td>
<td>131</td>
<td></td>
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<tr>
<td>mean baseline GFR ± SD (range) [ml/min]</td>
<td>37.1 ± 23.8 (2 to 104)</td>
<td>31.3 ± 23.1 (6 to 91)</td>
<td>35.5 ± 28.1 (6 to 115)</td>
<td>13.2 ± 10.9 (1 to 27)</td>
<td>123</td>
<td></td>
</tr>
<tr>
<td>No. studied</td>
<td>65</td>
<td>19</td>
<td>22</td>
<td>17</td>
<td>132</td>
<td></td>
</tr>
<tr>
<td>mean systolic BP ± SD (range) [mm Hg]</td>
<td>161.3 ± 28.7 (90 to 220)</td>
<td>179.5 ± 26.6 (132 to 238)</td>
<td>166.6 ± 24.7 (120 to 220)</td>
<td>170.6 ± 37.9 (120 to 240)</td>
<td>NS</td>
<td></td>
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<tr>
<td>mean diastolic BP ± SD (range) [mm Hg]</td>
<td>85.7 ± 14.7 (60 to 140)</td>
<td>98.2 ± 15.5 (76 to 140)</td>
<td>87.0 ± 17.3 (50 to 120)</td>
<td>91.5 ± 22.4 (60 to 134)</td>
<td>0.033</td>
<td></td>
</tr>
<tr>
<td>No. studied</td>
<td>73</td>
<td>19</td>
<td>22</td>
<td>17</td>
<td>132</td>
<td></td>
</tr>
<tr>
<td>hypertensive</td>
<td>64 (87.7)</td>
<td>18 (95.0)</td>
<td>20 (90.9)</td>
<td>14 (82.4)</td>
<td>119 (90.2)</td>
<td>NS</td>
</tr>
<tr>
<td>No. studied</td>
<td>65</td>
<td>19</td>
<td>21</td>
<td>12</td>
<td>117</td>
<td></td>
</tr>
<tr>
<td>mean n of antihypertensive drugs ± SD (range)</td>
<td>2.2 ± 1.0 (1 to 5)</td>
<td>2.3 ± 1.0 (1 to 4)</td>
<td>2.8 ± 0.8 (1 to 4)</td>
<td>2.3 ± 1.1 (1 to 5)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>No. studied</td>
<td>80</td>
<td>19</td>
<td>26</td>
<td>17</td>
<td>143</td>
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<tr>
<td>diabetes mellitus</td>
<td>12 (15)</td>
<td>3 (16)</td>
<td>0</td>
<td>0</td>
<td>15 (10.5)</td>
<td>NS</td>
</tr>
<tr>
<td>No. studied</td>
<td>73</td>
<td>19</td>
<td>22</td>
<td>17</td>
<td>132</td>
<td></td>
</tr>
<tr>
<td>ischemic heart disease</td>
<td>24 (32.9)</td>
<td>9 (47)</td>
<td>14 (63.6)</td>
<td>10 (58.8)</td>
<td>57 (43.2)</td>
<td>&lt;0.05</td>
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<tr>
<td>left ventricular failure</td>
<td>13 (17.8)</td>
<td>6 (32)</td>
<td>7 (31.8)</td>
<td>6 (35.3)</td>
<td>32 (24.2)</td>
<td>NS</td>
</tr>
<tr>
<td>peripheral vascular disease</td>
<td>39 (52.7)</td>
<td>11 (58)</td>
<td>13 (59.1)</td>
<td>7 (41.2)</td>
<td>70 (53.0)</td>
<td>NS</td>
</tr>
<tr>
<td>TIA or CVA</td>
<td>7 (9.9)</td>
<td>10 (53)</td>
<td>6 (27.3)</td>
<td>2 (11.8)</td>
<td>27 (20.5)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>any vascular disease</td>
<td>48 (65.8)</td>
<td>15 (79)</td>
<td>17 (77.3)</td>
<td>12 (70.6)</td>
<td>92 (70.0)</td>
<td>NS</td>
</tr>
<tr>
<td>No. studied</td>
<td>43</td>
<td>11</td>
<td>12</td>
<td>9</td>
<td>75</td>
<td></td>
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<tr>
<td>mean urinary protein ± SD (range) [g/24 hr]</td>
<td>1.18 ± 1.90 (0.1 to 8.2)</td>
<td>1.20 ± 1.56 (0.05 to 5.4)</td>
<td>0.79 ± 1.06 (0.06 to 3.4)</td>
<td>1.36 ± 1.04 (0.20 to 2.7)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>No. studied</td>
<td>57</td>
<td>12</td>
<td>16</td>
<td>14</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>mean renal size ± SD (range) [cm]</td>
<td>10.6 ± 1.7 (7.7 to 14.0)</td>
<td>10.3 ± 1.2 (7.9 to 12.9)</td>
<td>9.8 ± 1.1 (7.3 to 11.0)</td>
<td>9.1 ± 1.1 (7.5 to 11.4)</td>
<td>0.005</td>
<td></td>
</tr>
</tbody>
</table>

*a* Values are n (%) unless otherwise indicated.

RAO, renal artery occlusion; RAS, renal artery stenosis.
a history of myocardial infarction and/or angina, 24% cardiac failure, 53% peripheral vascular disease, and 21% cerebrovascular disease at the time of angiography. Ischemic heart disease was significantly more likely in patients with severe contralateral RAS or bilateral RAO, but the comorbid prevalence of peripheral vascular disease was similar in the four subgroups.

Baseline Renal Function and Progression of Renal Dysfunction

The mean serum creatinine of the overall RAO patient group was $277 \pm 239 \, \mu\text{mol/L}$ and the mean GFR $33.2 \pm 24.4 \, \text{ml/min}$; this compared with a creatinine of $246 \pm 204 \, \mu\text{mol/L}$ and GFR of $38.2 \pm 25.6 \, \text{ml/min}$ for the 157 patients with ARVD who did not have RAO (NS). Figure 1 illustrates the baseline serum creatinine of patients with RAO, again grouped according to contralateral renovascular disease severity. Even patients with normal contralateral vessels had advanced renal failure (serum creatinine, $243 \pm 235 \, \mu\text{mol/L}$; GFR, $37.1 \pm 23.8 \, \text{ml/min}$), but renal function was no worse than that in the subgroup with severe contralateral RAS. As expected, patients with bilateral RAO had significantly worse renal function (creatinine, $540 \pm 304 \, \mu\text{mol/L}$ $[P < 0.0001]$; GFR, $13.2 \pm 10.9 \, \text{ml/min}$ $[P < 0.0006]$) than the other subgroups. One patient with bilateral RAO had well-preserved renal function (creatinine, $189 \, \mu\text{mol/L}$; GFR, $27 \, \text{ml/min}$); this patient had extensive bilateral collateral renal circulations that developed as a consequence of slowly worsening bilateral stenoses.

In Figure 2, patients are divided into subgroups of renal dysfunction within each category of contralateral renovascular disease. In patients with bilateral RAO, no patients had mild and 20% had moderate renal dysfunction, but these categories (combined) were evident in 58% (contralateral significant RAS), 53% (RAS <50%), and 64% (patent contralateral vessel) of the other respective subgroups. Conversely, 8% of patients with contralateral normal vessels and 11% with insignificant contralateral RAS still presented with ESRF, although the proportion was much greater in patients with bilateral RAO (53%). Furthermore, the proportion of patients with severe dysfunction was very similar in all four subgroups (27% to 40%).

Follow-up renal functional data were available in 100 patients with RAO (Table 2); no follow-up data were possible for the remaining 38 patients because 9 had presented as requiring dialysis, 27 died or progressed to dialysis within 3 mo of angiographic diagnosis, and 2 were lost to follow-up. The overall mean follow-up time for the renal functional assessments was $31.0 \pm 20.7 \, \text{(1 to 82) mo}$; the mean follow-up times were similar in all subgroups. The overall rate of decline of GFR was relatively slow ($\sim 4.1 \, \text{ml/min per yr}$), and although patients in the contralateral insignificant subgroup trended to greater deterioration ($\sim 7.8 \, \text{ml/min per yr}$), this change was statistically insignificant because of the wide variations within each subgroup. This pattern of renal functional deterioration was further highlighted by consideration of the proportion of patients whose GFR fell by $>20\%$ during follow-up. Overall, 52% deteriorated in this way; however, comparison among the four subgroups indicated that patients with insignificant contralateral RAS had a greater likelihood of deterioration (64%) compared with patients with contralateral normal (45%) and significant RAS (53%); 82% of patients with bilateral RAO deteriorated.

These results show that, with the exception of patients with bilateral RAO, the degree of baseline renal dysfunction does not relate to the overall severity of proximal ARVD. Similarly, the progression of renal dysfunction appears to be independent of contralateral renovascular anatomy in patients with RAO.
Revascularization Procedures

During the period of study, only a small number of patients were subjected to a renal revascularization procedure, and all of these took place during the last 5 yr of the study. Eight patients (5.4%) underwent percutaneous renal angioplasty, which was technically successful in only four; only one of these patients received an endoluminal stent. These four patients all had RAO with contralateral severe RAS (two had 60% and the others 70% and 90%, respectively). All patients had stable renal function (mean baseline GFR, 41.4 ± 11.0 ml/min; change in GFR, −0.8 ± 0.8 ml/min per yr) at the latest follow-up (mean 40.5 ± 10.3 mo).

Relationship of Renovascular Anatomy and Renal Function to Ultrasound Renal Size and Proteinuria

The bipolar renal lengths of the contralateral kidneys followed the pattern of renal dysfunction in the subgroups (Table 1). Hence, contralateral RAO kidneys were significantly smaller (9.1 ± 1.1 cm) than those of patients with normal contralateral vessels (10.6 ± 1.7 cm; P < 0.005), but there were no significant differences among the other subgroups. However, when contralateral renal size was correlated against GFR for all patients (Figure 3), a very close relationship was observed (r = 0.44; P < 0.0001). Again, although the 24-h urinary protein excretion, a likely marker of intrarenal damage, also did not vary significantly among subgroups, when the complete patient population was considered, there was an overall correlation with GFR (r = −0.32; P < 0.01). Four patients had nephrotic-range proteinuria, and all of these patients had GFR <10 ml/min in association with either contralateral normal or insignificant RAS. Because these were

![Figure 3. Correlation regression for baseline GFR and contralateral renal size. Contralateral renal bipolar length (cm) was significantly related to GFR (r = 0.44; P < 0.0001).](image_url)
solitary functioning kidneys, renal biopsies were not performed.

**Dialysis and Mortality Outcomes**

Nine patients (6.1%) were already receiving dialysis at the time of angiography, and a further 15 (10.5% of the remainder) required RRT during follow-up. These latter patients all had severe baseline renal dysfunction (creatinine, 534 ± 210 µmol/L; GFR, 12.9 ± 8.1 ml/min). Two additional patients refused RRT. Dialysis need reflected the pattern of baseline renal function, with proportionately more patients with contralateral insignificant RAS receiving dialysis (40%) than those with significant RAS or contralateral normal (11.5% and 11.3%, respectively; \( P < 0.03 \)).

Deaths occurred in 85 patients (59.9%) during the period of study, which compared with 67 (42.9%) of the 157 patients without RAO in the ARVD database. The 5-yr survival of all the RAO patients was 31%, with an overall median survival of 25 mo. Again, with the exception of patients with bilateral RAO (of whom the majority died within the initial hospital admission after diagnosis, irrespective of institution of dialysis), there was no relationship between mortality and severity of contralateral renovascular disease. Hence, median survival was actually greatest in patients with either contralateral normal (57 mo, 5-yr survival 69%) or >50% RAS (32 mo, 5-yr survival 39%) and the least in those with bilateral RAO (<1 mo); median survival was, surprisingly, only 21 mo in those with contralateral RAS <50%. The combined end points of death and dialysis need are illustrated in Figures 4 and 5. The worst outcomes were evident in patients with bilateral RAO and contralateral insignificant RAS, in whom median survival without dialysis was 0 and 6 mo, respectively (Figure 4). However, this survival pattern actually reflects the baseline renal function of the four subgroups, and the inverse relationship between advancing renal dysfunction and survival is further emphasized in Figure 5. As would be expected, dialysis-free survival was greatest in patients with well-preserved GFR at baseline.

Proportional hazards regression confirmed that the probability of death or dialysis need in patients with RAO was significantly increased in those with contralateral insignificant RAS and bilateral RAO (Table 3). However, the multivariate models clearly show that baseline renal function was the more important determinant of outcomes. **Table 3.** Adjusted Cox proportional-hazards analysis of association between baseline factors and combined end point of mortality or dialysis need

<table>
<thead>
<tr>
<th>Relative Risk</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per yr)</td>
<td>1.007 (0.980 to 1.036)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.94 (0.98 to 1.04)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>1.29 (0.68 to 2.41)</td>
</tr>
<tr>
<td>Contralateral renal artery anatomy</td>
<td></td>
</tr>
<tr>
<td>normal (reference)</td>
<td>1</td>
</tr>
<tr>
<td>insignificant RAS</td>
<td>3.39 (1.66 to 6.90)</td>
</tr>
<tr>
<td>(≤50%)</td>
<td></td>
</tr>
<tr>
<td>significant RAS</td>
<td>0.95 (0.43 to 2.13)</td>
</tr>
<tr>
<td>(&gt;50%)</td>
<td></td>
</tr>
<tr>
<td>RAO</td>
<td>1.09 (0.34 to 3.48)</td>
</tr>
<tr>
<td>GFR groupings</td>
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<tr>
<td>&gt;50 ml/min (reference)</td>
<td>1</td>
</tr>
<tr>
<td>25 to 50 ml/min</td>
<td>1.41 (0.52 to 3.84)</td>
</tr>
<tr>
<td>10 to 25 ml/min</td>
<td>4.40 (1.63 to 11.89)</td>
</tr>
<tr>
<td>&lt;10 ml/min</td>
<td>29.22 (5.53 to 154.5)</td>
</tr>
</tbody>
</table>

* The variables included were contralateral renal anatomy, age, diabetes mellitus, ischemic heart disease, and GFR grouping.
tant prognostic variable, with renal vascular anatomy having no additional, or independent, prognostic impact.

Discussion

This epidemiologic study included both a retrospective and a prospective arm, which highlights the time required to assemble such a large study population of patients with RAO. Although it would have been preferable to have reported only prospectively collected data, we felt that it would have been some time before we could reliably report on outcomes in this smaller group. Nevertheless, the outcome analyses provide further important insights into the pathogenesis of renal dysfunction and likelihood of mortality in patients with ARVD. The key findings were threefold. First, the severity of renovascular disease in the kidney contralateral to the RAO was not predictive of the extent of baseline renal dysfunction (with the exception of bilateral RAO), which emphasizes the importance of intrarenal parenchymal damage, rather than the hemodynamic effects of a given stenosis, in the pathogenesis of renal dysfunction in the majority of patients with ARVD. Furthermore, the severity of renal dysfunction at the time of ARVD diagnosis, rather than contralateral renovascular anatomy or even a history of comorbid ischemic heart disease, was clearly the best predictor of future mortality, the latter being greatest in patients with severe renal failure. Third, there was a surprisingly low rate of progression of this high-risk group through to ESRF during follow-up.

In this unit, data have been recorded since 1987 in all patients proved by angiography to have ARVD. Renal revascularization procedures have only been performed in a minority of patients during this time (5.6% of the patients with RAO). This low revascularization rate derives from the fact that prospective randomized trials (which might show a benefit of renal revascularization to patient survival or renal functional prognosis) have been absent from the renovascular literature. These studies are now eagerly awaited. However, we have accordingly accumulated a large population of nonrevascularized patients with ARVD in which to study the natural history of renal dysfunctional progression and mortality. Appraisal of the basic epidemiologic characteristics shows a high prevalence of patients with RAO (47.5% of the total ARVD population), which reflects that the primary indication for renal angiography in the majority of our patients was for investigation of renal impairment rather than of isolated hypertension. Other studies of patients with ARVD with renal failure have found similar RAO prevalence (15). Extrarenal vascular disease was evident in 68.7% of all patients with RAO, and the prevalence of ischemic heart disease (43%) (18,19) and peripheral vascular disease (52%) (20–22) were also comparable with the existing ARVD literature.

The few previous studies in the literature that involved patients with RAO have concentrated on the effects of revascularizing the occluded kidney (23–25). However, the study of patients with RAO provides an ideal opportunity to further understand the pathogenesis of renal dysfunction in ARVD because, theoretically at least, differences in baseline renal function and eventual renal functional outcome are mainly dependent on changes in the kidney contralateral to the RAO. The findings in this investigation further support the view that intrarenal parenchymal damage, rather than significant hemodynamic perturbation consequent upon a tight stenosis, is the arbiter of renal dysfunction in the majority of patients with ARVD (12). Hence, and with the understandable exception of patients with bilateral RAO, when patients were analyzed in subgroups that were determined by contralateral renal artery anatomy, there was no significant difference in mean baseline renal function among the groups. If anything, there was a trend toward renal function being worse in patients with insignificant contralateral RAS compared with those with significant RAS. One hypothesis to explain the latter is that a tight stenosis can be protective by minimizing intrarenal damage from systemic influences (hypertension or atheroemboli) in the kidney downstream from the lesion (26). Furthermore, it should be noted that a larger proportion of patients with insignificant, compared with significant, contralateral disease presented with ESRF and that mean baseline GFR was already low (only 37 ml/min) in the patients with a normal contralateral vessel. Both observations again emphasize the importance of renal parenchymal injury in the pathogenesis of renal dysfunction in ARVD. Isotopic studies that measure SK-GFR further clarify this point, because SK-GFR may be similar in the paired kidneys from patients who have high-grade unilateral RAS and normal contralateral vessels (13).

Our findings are in keeping with the variable renal functional outcomes that are known to accompany renal revascularization procedures in ARVD. When patients with RAS lesions have their renal artery narrowing corrected by angioplasty with (9,27–29) or without a stent (7,8) or by vascular surgery (10,11,30,31), only a minority manifest improved renal function, and these are presumably the patients who genuinely do have potentially reversible renal dysfunction consequent to ischemia induced by the stenosis (26). Investigation with SK-GFR provides further insight—angioplasty of a tight atherosclerotic stenosis usually does not increase the individual function of the affected kidney (13), whereas SK-GFR is increased after revascularization of fibromuscular lesions in younger patients, presumably because the renal parenchyma beyond the stenosis is healthy in this condition.

Long-term follow-up of patients with RAO showed a relatively low overall rate of decline in renal function and no significant differences among the subgroups with differing contralateral anatomy (e.g., GFR fell by 2.3 to 8.2 ml/min per yr). Indeed, although nine of these high-risk patients were already in need of RRT at the time of initial presentation, surprisingly only 11% of the remaining patients were found to progress to ESRF during follow-up, and these all had severe renal dysfunction at baseline. Similar modest declines of renal function have been shown elsewhere, albeit in more heterogeneous groups of patients with ARVD (32,33). Although angiographic follow-up was not performed in our study, this low rate of progressive renal dysfunction implies that the likelihood of developing contralateral RAO during follow-up must accordingly be relatively low or that our current basic renoprotective strategies (which include hypertension control and use of as-
pirin and statins) can be effective in moderating progressive renal dysfunction.

Two further observations support the predominant role of intrarenal damage in causing the renal impairment in patients with ARVD. We found that both the extent of proteinuria and the contralateral renal bipolar length, measured by ultrasound at baseline, correlated with GFR but not with renovascular anatomy. Nephrotic-range proteinuria was observed in four of the patients, but renal biopsies were not performed because these were solitary functioning kidneys. Although their proteinuria may possibly have been due to either cholesterol atheroembolic disease or focal segmental glomerulosclerosis, proteinuria has been shown to be a nonspecific marker of parenchymal damage in patients with ARVD, and it increases with declining GFR in this condition (34). Serial duplex ultrasound has been used by Caps et al. (35) to determine which factors increase progression to renal atrophy in ARVD. Their findings, that the cumulative risk of atrophy was greatest in patients with poorly controlled hypertension and that atrophy of kidneys with RAS >60% was usually not due to development of RAO, are consistent with those of this study.

Patients with ARVD have a high relative mortality (33,36,37), which is partly explained by a comorbid association with extrarenal vascular disease (38). We found that survival was comparable between the two groups of patients with ARVD, both with and without RAO. The most striking determinant of mortality in patients with RAO was their renal function. Hence, although overall median survival was 25 mo in patients with RAO, 69% of patients with baseline GFR >50 ml/min were likely to be alive at 5 yr, whereas those patients who presented with a GFR of only 10 to 25 ml/min had a median survival of only 17.7 mo, and patients who presented with ESRF had extremely poor survival (median <1 mo). Other studies have shown that patients with the most extensive renovascular lesions have the greatest mortality rate (15). Although unadjusted subgroup analysis of our patients with RAO appeared to lend support to this view (especially those patients with bilateral RAO, who had a high initial mortality rate), when mortality was adjusted for baseline renal function, contralateral renal artery anatomy was found to be relatively unimportant. The relative risk of mortality was significantly increased in patients with baseline GFR <25 ml/min, and this effect was amplified in patients who presented with ESRF.

In summary, we have shown that patients with RAO have a greatly increased risk of mortality if they have moderate to severe renal failure. Intrarenal damage in the kidney contralateral to the RAO appears to be a major contributor to the pathogenesis of the renal failure in these patients. By inference, future therapeutic strategies in these high-risk patients should be aimed at minimizing intrarenal damage before renal failure supervenes. Large-scale trials are also now warranted in patients with ARVD, with the hope that those subgroups most likely to gain renal functional and mortality benefits from revascularization procedures can be identified.

References


