Renovascular disease: Effect of ACE gene deletion polymorphism and endovascular revascularization

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In selected populations renal artery stenosis (RAS) is a relatively common hypertensive disorder characterized by significant clinical complications such as resistant hypertension, recurrent pulmonary edema, and ischemic nephropathy, which in turn give rise to high cardiovascular mortality.1-3 Five years after diagnosis, progression of luminal narrowing occurs in 51% of patients and renal artery occlusion occurs in 5% of patients; renal atrophy develops in 20% of patients after 2 years.4,5 The mortality rate in patients with bilateral RAS is 38% after 2 years5; in patients with end-stage renal disease due to RAS, it is 80% after 5 years6, and in patients with RAS and coronary artery disease it is 67% after 4 years.7

Surgical treatment of RAS has been used extensively, with satisfactory results but with relatively high perioperative mortality and morbidity. Percutaneous transluminal renal angioplasty (PTRA) alone or in combination with stent implantation (PTRA-S) is a valid alternative to surgery.

Despite availability of these less invasive techniques and the severe prognosis with RAS, determination of which patients should undergo revascularization and the timing of the procedure are still matters of controversy. In noncontrolled trials, improved blood pressure and control and stabilization of renal function were observed after restoration of luminal patency.8-11 Nevertheless, the only three randomized controlled trials comparing PTRA and conservative medical therapy showed no significant differences in outcome and a number of PTRA-related complications,12-14 which suggests caution in extensive PTRA treatment.

Genetic predisposition may contribute to the pathogenesis of RAS, and identification of the gene variants involved in the pathogenesis may improve prognosis and therapy. In recent years, attention has been focused on the possible association with insertion/deletion (I/D) polymorphism of the angiotensin converting enzyme (ACE) gene. Several studies have reported a higher frequency of DD homozygosity in patients with RAS (on average, DD genotype, 49%; range, 41%-54.5%) than is usually reported for the general population (on average, 30%-32%).15-17 In addition, Losito et al18 reported a higher mortality rate in patients with this genotype compared with patients with other genotypes (6-year survival, 45.4% vs 73.4%). Inasmuch as ACE I/D polymorphism is a major determinant of circulating ACE, with higher serum levels in subjects homozygous for the D allele,19 activation of the renin-angio-
tensin system and production of angiotensin II may be exaggerated in DD carriers.

The purpose of the present study was to evaluate possible interactions between ACE I/D polymorphism, type of treatment, and complications, including mortality, associated with RAS.

MATERIAL AND METHODS

Patients. Records for all patients with angiographically significant RAS (>50%) identified from May 1996 to May 2002 at our institution were retrospectively examined for the study. One hundred twenty-two patients were initially recruited. Most of the patients underwent angiographic evaluation, because of high or moderate index of clinical suspicion for renovascular hypertension according to Mann and Pickering criteria

or because of suggestive findings at Doppler ultrasound scanning. These patients generally had severe hypertension, requiring two or more drugs, in association with clinically evident atherosclerosis in other regions, mainly the coronary arteries and lower extremities, or some degree of renal impairment. A second group of patients with hypertension was enrolled because of significant RAS recognized at angiographic evaluation performed for other causes, mainly lower extremity vascular disease.

At baseline angiography, 226 renal arteries were studied, and 127 significant stenoses were detected.

Patients with nonatherosclerotic RAS (8 patients with fibrodysplasia, 2 patients with vasculitis) and patients with insufficient follow-up data (12 patients did not have at least one follow-up examination) were excluded. Records for 100 patients were finally considered suitable for statistical analysis.

The study was approved by our institutional review board, and all patients gave informed consent.

Treatment. Two groups of patients were observed. Thirty-seven patients received conservative therapy (CT group). In these patients, the diagnosis was first made at angiographic evaluation performed because of other causes, usually lower extremity arteriopathy, in the Vascular Surgical Department at our hospital. As the primary therapeutic goal was not renovascular disease, but arterial insufficiency of the legs, the possibility of renal endovascular therapy was not considered for most patients in this group.

In a number of patients in this group, the possibility of PTRA or PTRA-S was excluded because of cardiac conditions, such as symptomatic coronary artery disease (CAD). Sixty-three patients received endovascular therapy (ET group). This group of patients was first evaluated because of resistant hypertension or unexplained azotemia, and the diagnosis was made in our Hypertension Unit. Of the patients with RAS considered as a whole, 48% had CAD, and 78% and 59%, respectively, had ultrasonic or angiographic evidence of carotid or lower extremity artery disease. The relative percentages of areas of vascular disease in the CT and ET groups are reported in Table I. CAD was diagnosed on the basis of clinical findings (typical symptoms requiring specific therapy) or instrumental evidence (resting or exercise-induced electrocardiographic alterations, coronary angiography). Peripheral arterial disease (carotid artery or lower extremities) was diagnosed on the basis of ultrasonic or angiographic evidence of one or more areas of stenosis resulting in at least 50% reduction in the vessel lumen.

At baseline angiography, 29.5% of the CT group and 26.5% of the ET group had greater than 50% stenosis bilaterally, and subocclusive lesions were detected in 36.1% and 40.6% of patients, respectively, in the two groups. In the population as a whole, stenosis was ostial in 52.6% of cases and located in the proximal third of the vessel in the remaining cases.

All of these patients were subsequently recalled and examined at scheduled follow-up visits, and venous blood samples for genetic analysis were collected after obtaining informed consent. Patients in both groups received the least number of hypotensive drugs to adequately control blood pressure (target blood pressure ≤140/90 mm Hg). The most frequently used classes of drugs were ACE inhibitors (62% of patients), diuretics (furosemide in 46.7%, other diuretics in 15.2% of patients), calcium antagonists (48.9% of patients), and β-blockers (30.4% of patients).

There was no statistically significant difference in percentage of any single class of drugs between the two groups of patients (data not shown).

Until 1999, renal artery interventions generally consisted of PTRA, and stent implantation (Palmaz model) was performed only in patients in whom PTRA results were unsatisfactory. Since 1999, all patients have undergone revascularization with primary PTRA-S (Corinthias model; stent diameter, 4-7 mm). Of 63 patients who underwent revascularization, PTRA was performed in 32.8%, and PTRA-S in 67.2%.

Immediate complete success of a procedure was defined when less than 50% residual artery stenosis was obtained. All procedures were successful. After PTRA-S, patients received heparin intravenously for 24 hours, and antiplatelet therapy was given indefinitely.

Procedural complications included partial renal infarction (superior pole) (n = 2), cholesterinic embolism in the lower extremities (n = 1), non-Q myocardial infarction (n = 1), and acute worsening of preexisting renal insufficiency (n = 2). It should be noted that three of these complications occurred in the same patient.

Follow-up. Clinical, biochemical, and radiologic follow-up data were available for a median period of 28 months (range, 1-60 months), and the findings were compared with patient information collected at diagnosis (CT group) or just before PTRA-S (ET group).

Outcome in terms of blood pressure response was classified as follows. Hypertension was considered cured when blood pressure was less than 140/90 mm Hg without use of antihypertensive medication; improved when there was either a decrease in diastolic or systolic blood pressure of at least 10% with the same or fewer medications, or no change in blood pressure with fewer drugs; and worsened when there was either an increase in diastolic or systolic
Table I. Baseline characteristics of RAS patient population, subdivided by treatment method

<table>
<thead>
<tr>
<th>Variable</th>
<th>Endovascular treatment (n = 63)</th>
<th>Conservative treatment (n = 37)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>65.9 ± 8.5</td>
<td>69.5 ± 8.5</td>
<td>&lt;.05*</td>
</tr>
<tr>
<td>Smoker</td>
<td>40/23</td>
<td>27/10</td>
<td>NS†</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>168.2 ± 22.3</td>
<td>158.9 ± 27.33</td>
<td>NS‡</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>95.32 ± 10.18</td>
<td>90.54 ± 12.35</td>
<td>&lt;.05*</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>217.75 ± 47.56</td>
<td>211.52 ± 49.88</td>
<td>NS*</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>148.1 ± 35.96</td>
<td>151.2 ± 43.31</td>
<td>NS*</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>45.63 ± 10</td>
<td>41.37 ± 11.21</td>
<td>&lt;.05*</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>178.03 ± 77.05</td>
<td>195.74 ± 126.66</td>
<td>NS†</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.7 ± 1.1</td>
<td>6.5 ± 3.33</td>
<td>NS‡</td>
</tr>
<tr>
<td>Diabetes</td>
<td>19 (31.1)</td>
<td>14 (37.8)</td>
<td>NS‡</td>
</tr>
<tr>
<td>Uric acid (mmol/L)</td>
<td>0.37 ± 0.11</td>
<td>0.35 ± 0.1</td>
<td>NS*</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.46 ± 0.72</td>
<td>1.44 ± 0.69</td>
<td>NS†</td>
</tr>
<tr>
<td>Chronic renal failure§</td>
<td>20 (31.7)</td>
<td>11 (30.6)</td>
<td>NS†</td>
</tr>
<tr>
<td>Homocysteine (µmol/L)</td>
<td>21.53 ± 18.31</td>
<td>23.26 ± 14.76</td>
<td>NS‡</td>
</tr>
<tr>
<td>Antihypertensives drugs</td>
<td>2.41 ± 1.12</td>
<td>2.14 ± 1.67</td>
<td>NS‡</td>
</tr>
<tr>
<td>Renal artery lumen reduction (%)</td>
<td>50–75 26 (40.6)</td>
<td>14 (38.9)</td>
<td></td>
</tr>
<tr>
<td>75–90</td>
<td>36 (56.3)</td>
<td>9 (25)</td>
<td></td>
</tr>
<tr>
<td>Subocclusive</td>
<td>18 (29.5)</td>
<td>9 (26.5)</td>
<td>NS‡</td>
</tr>
<tr>
<td>Bilateral RAS</td>
<td>26 (43.3)</td>
<td>22 (61.1)</td>
<td>NS‡</td>
</tr>
<tr>
<td>Peripheral arteriopathy (%)</td>
<td>Lower extremities 50.9 72.2</td>
<td>9 (25)</td>
<td>&lt;.05†</td>
</tr>
<tr>
<td>Carotid artery</td>
<td>61.4</td>
<td>52.8</td>
<td>NS†</td>
</tr>
<tr>
<td>Lower extremities and carotid artery</td>
<td>78.9</td>
<td>77.8</td>
<td>NS†</td>
</tr>
<tr>
<td>ACE genotype (%)</td>
<td>II 18.5</td>
<td>10</td>
<td>NS†</td>
</tr>
<tr>
<td>ID 35.2</td>
<td>33.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD 46.3</td>
<td>56.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Endovascular treatment = revascularization with percutaneous transluminal renal angioplasty, with or without stenting. Stenosis grade reported for main stenosis in patients with bilateral stenosis.

Numbers in parentheses represent percent.

RAS, Renal artery stenosis; BP, blood pressure; LDL, low-density lipoprotein, HDL, high-density lipoprotein; CAD, coronary artery disease

* Mann-Whitney nonparametric test.

† Student t test for qualitative variables.

‡ Student t test.

§ Creatinine concentration > 1.5 mg/dL.

Blood pressure of at least 10% with the same or more drugs, or no change in blood pressure with more drugs. In all other cases blood pressure was considered unchanged.21,22

Renal function was considered improved when a decrease in serum creatinine (Cr) concentration of at least 0.2 mg/dL (17.7 µmol/L) was observed, worsened when serum Cr concentration increased by at least 0.2 mg/dL, and unchanged when variation was less than 0.2 mg/dL.22

Renal artery patency was checked at angiography or echo Doppler ultrasound scanning in the ET group. Recurrent stenosis was angiographically defined as reduction in lumen diameter of at least 50% in a previously revascularized renal artery. When patency was checked with echo Doppler scanning and recurrent stenosis was suspected, renal angiography was systematically repeated for confirmation.

Mutation analysis.

Genomic DNA was extracted from whole blood with standard methods.

To determine ACE genotype, genomic DNA was amplified with polymerase chain reaction with the hace3 primer pair. Each sample with the DD genotype was subjected to a second independent polymerase chain reaction amplification with the hace5 primer pair, which recognized only the I allele.16

Statistical analysis. Data analysis was performed with SPSS version 10.0 for Windows (SPSS, Chicago, Ill). Quantitative values were expressed as mean ± SD. The Student t test for unpaired observations was used for normally distributed variables, and the Mann-Whitney U test for nonnormally distributed variables. Comparison of proportions was carried out with cross-tabulation, Pearson χ² test, and Fisher exact test.

To define which baseline variables could serve as useful predictors of subsequent clinical outcome, various multivariate regression models were used. For survival, analysis was performed with the Cox proportional hazards regression model. A logistic regression model was used for the other three main clinical outcomes: blood pressure control (improved vs unchanged or worsened), renal function (worsened vs unchanged or improved), and arterial recurrent stenosis (yes or no). Only variables achieving a level of
significance of 0.1 were included in the final multivariate models.

For ACE I/D polymorphism, dummy variables were created for the various genotypes, with the II genotype as reference. To detect a possible specific role of the DD genotype, a model using II and ID as reference was also used.

RESULTS

Characteristics of study population

Baseline characteristics of the study population, that is, the ET group (n = 63) and the CT group (n = 37), are shown in Table I. The groups were generally well-matched for most clinical features, but differed in age, diastolic blood pressure, high-density lipoprotein cholesterol, and prevalence of lower extremity atherosclerosis. Although a high frequency of DD genotype was observed in the population as a whole (II 15.8%, ID 35.8%, DD 48.4%), there was no difference in ACE genotype distribution between the two groups.

Follow-up

Mortality. Seventeen patients (17%) died during follow-up, 15 as a result of major cardiovascular events, and 2 of neoplastic disease. These latter deaths were regarded as unrelated to RAS, and were not included in the survival analysis (Fig 1). The survival curve for 98 subjects, calculated over a median observation period of 28 months, is shown in Fig 1, A. Cumulative probability of survival was 93.51% after 1 year and 70.7% after 5 years. Fig 1, B shows survival curves for patients subdivided according to treatment group: at the end of follow-up, survival probability in patients who underwent PTRA or PTRA-S was 86.74%, compared with 67.13% for those in the CT group. Baseline clinical features, possibly associated with mortality, were tested with Cox regression analysis. Table II presents the variables that achieved a level of significance of 0.1 and were included in the final multivariate regression model. An independent predictor of survival was endovascular treatment, which was associated with a substantial reduction in mortality (hazard ratio, 0.31; 95% confidence interval [CI], 0.1-0.96; Table II). Baseline Cr concentration greater than 1.5 mg/dL was associated with lower probability of survival (P = .05; hazard ratio, 2.87; 95% CI, 1-8.27). Although a lower proportion of survivors had CAD at diagnosis (42.5% vs 86.7%; P < .01), the presence of CAD failed to prove statistically significant when adjusted for the other variables in the multivariate Cox model (Table II). Similarly, in the same model age was not a useful predictor of mortality. ACE DD genotype distribution was not associated with mortality (35.7% deceased and 49.4% surviving patients had the DD genotype; P = NS; Table III).

In the population as a whole, 47 patients (26 in the ET group and 21 in the CT group) had evidence of CAD. Endoscopic therapy still afforded an advantage in terms of survival in this subgroup; mortality was twice as high in the CT compared with the ET group (38.1% vs 19.2%), although because of the small size of the sample the difference is not statistically significant (P = .15).

Improvement in blood pressure. Hypertension was not cured in any our study patients, including those who underwent revascularization at PTRA or PTRA-S. However, during follow-up blood pressure improved significantly in a larger proportion of patients in the ET group than in the CT group (57.4% vs 29%; P < .05; Fig 2, A). Baseline clinical features possibly associated with blood pressure control are reported in Table II. Only treatment with PTRA or PTRA-S (odds ratio [OR], 3.21; 95% CI, 1.06-9.7) was associated with a significantly increased probability of blood pressure improvement in the final logistic regression model. Other variables tested, including
ACE DD genotype, were not associated with subsequent blood pressure control.

**Renal function.** About half of the patients (48.4%) in the CT group exhibited renal function deterioration during follow-up, confirming the view that ischemic nephropathy is a progressive disease (Fig 2, B). In contrast, during the same period, significant impairment of renal function was observed in only 17.9% of patients in the ET group. In the final logistic regression model, outcome was predicted only by revascularization treatment (OR, 3.65; 95% CI, 1.28-10.46) and age (OR, 0.91; 95% CI, 0.84-0.99; Table II). Baseline Cr concentration, diabetes, bilateral stenosis, and ACE DD genotype were not predictive of further functional worsening.

**Arterial recurrent stenosis.** Significant recurrent stenosis developed in 11 patients (21.6%) in the ET group. The rate of recurrent stenosis was higher in patients who underwent PTRA than in those who underwent PTRA-S (42.9% vs 18.5%), but the difference was not statistically significant ($P = .1$) because of the small number of patients. ACE DD genotype, bilateral RAS, blood pressure control, and cholesterol levels were not associated with a higher incidence of recurrent stenosis. Recurrent stenosis was generally associated with poor probability of improved blood pressure (22.2% of patients with recurrent stenosis vs 53.1% of patients without recurrent stenosis; data not shown).

**DISCUSSION**

We evaluated the clinical course in 100 patients with atherosclerotic RAS and analyzed factors associated with subsequent mortality, blood pressure control, decline in renal function, and arterial recurrent stenosis after a revascularization procedure. Three main results were obtained. First, the prognosis was poor in patients who did not undergo PTRA or PTRA-S but received conservative treatment with hypotensive drugs; 10 of 36 patients died, blood pressure was still inadequately controlled in 71%, and nearly half had worsened renal function (Figs 1, 2). Second, endovascular revascularization had a considerable effect on the course of renovascular disease, substantially reducing its adverse consequences (Fig 1; Table II). Finally, the DD genotype, though frequent in these patients, was not confirmed as predictive of mortality (Table III). This suggests that ACE DD may favor a mechanism that leads to development of arterial stenosis, but that the later clinical evolution of renovascular disease occurs independent of this genetic factor.

**Mortality rate.** Mortality in patients in the CT group was significantly higher than in the ET group. This result, however, requires critical interpretation. When planning the study, we exploited the opportunity offered by the various treatment strategies in two departments in our hospital after RAS detection at angiography. The two treatment groups, however, were not similar with regard to baseline variables. Because this was a retrospective study, patients included were not randomized for treatment, and the choice of therapy was based, at least in part, on individual clinical factors. There is, therefore, an element of bias inherent in this type of selection. When this limitation is taken into account, there still appears to be a favorable effect of ET on mortality from renovascular disease, for

### Table II. Regression models for main clinical outcomes

<table>
<thead>
<tr>
<th>Clinical outcomes</th>
<th>Baseline covariate</th>
<th>P</th>
<th>Hazard ratio</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cox proportional hazard regression</td>
<td>Percutaneous revascularization</td>
<td>&lt;.05</td>
<td>0.31</td>
<td>0.1-0.96</td>
</tr>
<tr>
<td>Death due to cardiovascular cause</td>
<td>Coronary artery disease</td>
<td>.07</td>
<td>4.52</td>
<td>0.91-20.58</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>.17</td>
<td>1.07</td>
<td>0.98-1.17</td>
</tr>
<tr>
<td></td>
<td>Basal serum creatinine &gt; 132.6 µmol/L</td>
<td>.05</td>
<td>2.87</td>
<td>1-8.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Logistic regression</td>
<td>Percutaneous revascularization</td>
<td>&lt;.05</td>
<td>3.21</td>
<td>1.06-9.7</td>
</tr>
<tr>
<td>Blood pressure improvement</td>
<td>Bilateral RAS</td>
<td>.06</td>
<td>3.23</td>
<td>0.97-10.83</td>
</tr>
<tr>
<td></td>
<td>Diastolic BP</td>
<td>.2</td>
<td>1.04</td>
<td>0.98-1.1</td>
</tr>
<tr>
<td>Stable or improved renal function</td>
<td>Number of antihypertensive drugs</td>
<td>.07</td>
<td>1.6</td>
<td>0.95-2.69</td>
</tr>
<tr>
<td></td>
<td>Percutaneous revascularization</td>
<td>&lt;.05</td>
<td>3.65</td>
<td>1.28-10.46</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>&lt;.05</td>
<td>0.91</td>
<td>0.84-0.99</td>
</tr>
<tr>
<td></td>
<td>Basal serum creatinine &gt; 132.6 µmol/L</td>
<td>.15</td>
<td>2.18</td>
<td>0.75-6.38</td>
</tr>
</tbody>
</table>

RAS, Renal artery stenosis; BP, blood pressure; CI, 95% confidence interval; OR, odds ratio.

### Table III. ACE I/D polymorphism distribution in relation to mortality

<table>
<thead>
<tr>
<th>Mortality (%)</th>
<th>ACE I/I</th>
<th>ACE I/D</th>
<th>ACE D/D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died</td>
<td>21.4</td>
<td>42.9</td>
<td>35.7</td>
</tr>
<tr>
<td>Survived</td>
<td>15.2</td>
<td>35.4</td>
<td>49.4</td>
</tr>
</tbody>
</table>

$P$ not significant ($chi^2$ test).
the following reasons. At multivariate logistic regression analysis, a protective role of ET was still observed after adjustment for all remaining covariates, including CAD prevalence; separate comparison of the 47 patients with renovascular disease, all similarly affected with CAD, demonstrated that ET was still capable of affording an advantage in terms of survival; the ET and CT patient groups were similarly affected by the main traditional risk factors, and the overall burden of vascular disease was similar in the two groups (Table I).

In a study of 3987 patients with CAD, presence of RAS was a strong independent predictor of mortality, and severity of arterial stenosis had an incremental effect on mortality. Although specific studies are lacking, our preliminary results suggest that patients with CAD with renovascular disease could particularly benefit from early renal revascularization.

The finding that baseline renal impairment is associated with higher mortality in RAS is in agreement with previous reports confirming that preservation of renal function is one of the main therapeutic goals.

The three controlled randomized trials that compared revascularization and medical therapy are an important reference in this field. However, duration of follow-up in two of the three trials was no longer than 12 months, with the result that conclusions about treatment and long-term RAS mortality could not be drawn. This is an important issue investigated in our study, and adds fresh material to the debate fuelled by conflicting results reported by others. Both neutral and unfavorable long-term clinical effect of conservative treatment on the natural history of RAS have been reported.

**Blood pressure control.** The only baseline patient feature associated with significant predictive power of subsequent blood pressure improvement was the revascularization procedure. In the context of the debate regarding the indication for endovascular therapy, our study provides evidence of better outcome after restoration of lumen patency compared with conservative therapy alone. Nevertheless, there is still no consensus as to which is the better treatment. Two of the most frequently cited studies are randomized controlled trials that compare conservative and endovascular treatment. In these studies, the two treatments showed no statistically significant difference in major outcome. However, in both cases the revascularization procedure was PTRA, which is associated with a high rate of recurrent stenosis, and a substantial proportion of patients assigned to drug therapy underwent balloon angioplasty after a few months, because of inadequate blood pressure control, thus making any long-term comparison impossible. These issues have therefore been criticized, and caution is warranted before any firm conclusion can be made.

**Renal function.** In our patients, endovascular therapy was associated with long-term stabilization or improvement in renal function. Despite similar baseline Cr concentration, long-term decline in renal function was observed in 17.9% of patients in the ET group compared with 48.5% in the CT group. This result was observed in a population with normal or slightly increased Cr concentration (1.46 ± 0.72 mg/dL; 70% of patients with Cr < 1.5 mg/dL), whereas in most published studies greater benefit was observed in patients with more severe renal impairment in patients with normal renal function, no significant decrease in Cr concentration has generally been described after endovascular therapy. In keeping with these results, only in a minority of our patients did Cr concentration decrease after PTRA or PTRA-S (21.4%), whereas in most patients...
renal function remained unchanged (60.7%). In other words, endovascular therapy “preserved” renal function against long-term progressive decline, as observed in the CT group. Thus our findings suggest that an early interventional approach may substantially delay progression of renal dysfunction, thus avoiding overt ischemic nephropathy and ultimately end-stage renal disease.

Recurrent stenosis. Evaluation of recurrent stenosis rate in patients in the ET group was not the primary purpose of our study because of the small number of patients who underwent revascularization, among other issues. The recurrent stenosis rate (18.5% and 42.9% in patients who underwent PTRA-S or PTRA, respectively) was similar to that reported by most authors, confirming PTRA-S as the best procedure. Worthy of note, in our patients recurrent stenosis was not associated with improvement in blood pressure, thus providing support for the positive role of renal artery patency in obtaining adequate blood pressure control.

ACE gene deletion polymorphism. Our data do not confirm the findings of Losito et al. of an association between the ACE DD genotype and higher mortality in patients with renovascular disease, despite similar genotype frequency and larger sample in our study. The different results could be related to the proportion of patients who undergo endovascular therapy in the two studies, but this cannot be compared because pertinent information is not provided by Losito and colleagues.

In our patients, the DD genotype was not associated with a decline in renal function, blood pressure control, or recurrent stenosis after PTRA or PTRA-S. It is possible that ACE inhibitors, which were used in a substantial proportion of our patients, might have limited production of angiotensin II (constitutively increased in patients with the DD genotype), thus reducing the clinical effect of ACE gene polymorphism. It is also reasonable to speculate that high concentration of angiotensin II, associated with the DD genotype, may initially favor the formation of atherosclerotic plaques, but that when hemodynamically significant arterial stenosis is established no further angiotensin II production is possible, regardless of ACE I/D genotype.

ADDITIONAL REMARKS

It is by no means easy to fully explain how revascularization can improve survival in patients with RAS, even when taking into account the important overall burden of vascular disease presented by most, if not all, of these patients. Preservation of renal function and better blood pressure control may be important mechanisms, but the extent of the changes does not appear sufficient to account for all the benefits observed in terms of survival. Some recently published contributions could be potentially important for understanding this problem. These findings suggest that in patients with renovascular hypertension excessive oxidative stress may be involved in systemic impaired endothelium-dependent vasodilation. Moreover, successful renal revascularization and consequent downregulation of the renin-angiotensin system decreases oxidative stress and improves systemic endothelium-dependent vasodilation. Therefore PTRA or PTRA-S may increase the general bioavailability of nitric oxide by inhibiting production of angiotensin and amplifying the “renal effect” at the systemic level. Of interesting, similar data have been obtained in atherosclerotic and fibrodyplastic artery stenosis, suggesting that vascular occlusion and renin-angiotensin system activation may prevail over the classic atherogenic risk factors.

CONCLUSIONS

Renovascular disease is a severe progressive condition associated with poor prognosis if untreated or detected late. The therapeutic measure most suited to delaying this unfavorable course is early endovascular revascularization, preferably with PTRA-S.

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REFERENCES
