Long-term follow-up of atherosclerotic renovascular disease. Beneficial effect of ACE inhibition

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Abstract

Background. Patients with atherosclerotic renovascular disease (ARVD) are almost invariably treated by revascularization. However, the long-term outcomes of this approach on survival and progression to renal failure have not been investigated and have not been compared with that of a purely medical treatment. The aim of this observational study was to investigate factors affecting long-term (over 5 years) outcome, survival and renal function of patients with ARVD treated invasively or medically.

Methods. ARVD was demonstrated angiographically in 195 patients who were consecutively enrolled into a follow-up study. Patient age was 65.6±11.2 years, serum creatinine was 1.74±1.22 mg/dl and renal artery lumen narrowing was 73.5±17.5%. A revascularization was performed in 136 patients, whereas 54 subjects having comparable characteristics were maintained on a medical treatment throughout the study; five patients were lost during follow-up.

Results. The main follow-up was 54.4±40.4 months. The assessment of cardiovascular survival and renal survival at the end of follow-up revealed 46 cardiovascular deaths, 20 patients with end-stage renal disease (ESRD) and 41 patients with an increase in serum creatinine of over one-third. The multivariate analysis showed that renal revascularization did not affect mortality or renal survival compared with medical treatment. Revascularization produced slightly lower increases in serum creatinine and a better control of blood pressure. A longer survival was associated with the use of angiotensin-converting enzyme inhibitors (ACEIs) (P=0.002) in both revascularized and medically treated patients. The only significant predictor of ESRD was an abnormal baseline serum creatinine.

Conclusions. On long-term follow-up, ARVD was associated with a poor prognosis due to a high cardiovascular mortality and a high rate of ESRD. In our non-randomized study, revascularization was not a major advantage over medical treatment in terms of mortality or renal survival. The use of ACEIs was associated with improved survival.

Keywords: angiotensin-converting enzyme inhibitors; end-stage renal failure; renovascular disease; revascularization; survival

Introduction

Atherosclerotic renovascular disease (ARVD) is being diagnosed with increasing frequency, especially in older patients with other vascular co-morbidities [1–3]. In recent years, many studies have assessed the effects of invasive approaches compared with standard medical treatments on the outcome of renovascular disease [4–6]. Both randomized studies and meta-analyses have shown only minor differences in clinical outcomes following medical treatment or revascularization during short-term or medium duration studies [7,8]. In addition, most studies measured blood pressure, renal function or both, whereas only a few assessed end-points such as cardiovascular mortality. Furthermore, survival analysis in these studies was not long enough to assess the benefits of the therapeutic methods accurately, which become clear only long after the intervention [9,10]. Therefore, sound data on outcomes after longer follow-ups (≥5 years) are not presently available. We undertook this study based on the hypothesis that the benefits of various treatments require a long time before they become visible and that these treatments can only be assessed by choosing definite end-points such as survival and end-stage renal disease (ESRD). We report here our findings from a cohort of 195 patients with renovascular disease during a follow-up of up to 189 months. Patients underwent either an endovascular correction.
of a renal artery stenosis or medical treatment. In this cohort, we examined outcomes in terms of blood pressure, renal function and survival, while analysing the effects of the two therapeutic approaches, as well as other factors.

Patients and methods

Patients

For this study, we enrolled all patients between 1992 and 2000 that had an atherosclerotic renal artery stenosis (lumen narrowing >50%), demonstrated by an arteriogram, and whose clinical data were available. Angiographic examination and revascularization were performed at the Angiographic Section of the Radiology Institute of the University of Perugia, Italy. The clinical and demographic characteristics of the 195 patients are shown in Table 1. Hypertension was present in 164 subjects and was treated with different classes of drugs, including β-blockers, calcium channel inhibitors and angiotensin-converting enzyme inhibitors (ACEIs). ACEIs were given to 62 patients. There were differences in blood pressure between patients on ACEIs and those without ACEIs, and this was independent of associations with other antihypertensive drugs. High cholesterol was present in 139 patients. Revascularization was performed. In addition, 136 patients, referred from different areas, were treated by regular use of statins in 41 patients (24 were smoking). The average renal artery stenosis on the whole cohort of patients was 73.5±17.5%. In 50 subjects, the stenosis was bilateral with an average lumen narrowing of 75.8±20.1% on the main side and of 66.3±13.5% on the secondary side. Serum creatinine was 1.62±1.08 mg/dl in monolateral and 2.06±1.50 mg/dl in bilateral disease.

The stenosis was proximal in 79.2%, ostial in 6.3% and distal in 14.6% of cases. Vascular disease in other areas was present in 139 patients. Revascularization was performed and stents were used in 41 patients (24 were treated invasively and 17 medically).

Assignment of treatment and follow-up

There was no selection in the choice of treatment. The criteria for assignment to the different treatments were based on the different clinical approaches used by the different referring units, and were not related to the characteristics of the patients. There were 54 patients referred to the renal unit (A.L. and R.E.) that were given only medical treatment (antihypertensive drugs, lipid-lowering if necessary, giving up smoking), unless an occlusive renal artery bilateral disease with need of dialysis was demonstrated (two patients). In these patients, an angioplasty with stent placement was performed. In addition, 136 patients, referred from different units that routinely performed angioplasty when renal stenosis is >50% at the time of angiography, were treated invasively (see below). Medical treatment was also given under the directions of the different physicians. For each patient, data relating to renal function, blood pressure, blood lipids and cardiovascular co-morbidity were recorded at the time of renal angiography. After the initial assessment, periodic out-patient evaluation, telephone consultation or both were made with an update of drug treatment. In the absence of complications needing hospitalization, patients living at short distances from the renal unit were assessed yearly on an out-patient basis, and the others were evaluated by telephone follow-up. Causes and dates of all deaths were also recorded. In August 2004, the follow-up was stopped. The interval between the last blood test and study conclusion was <6 months. Recorded cardiovascular events included angina or myocardial infarction, and transient ischaemic attacks or strokes. Deaths due to ischaemic heart disease, heart failure or cerebrovascular disease were recorded as having a cardiovascular cause.

Renal artery stenosis assessment

Angiographs of all patients were reviewed by two of our team (A.L. and R.E.) and were subsequently assessed for renal size and classified according to lumen narrowing. Grades of stenosis were 50–60, 60–75, 75–90 and >90%. Sites of stenosis were right or left artery, ostial, proximal or distal; monolateral or bilateral.

The average renal artery stenosis on the whole cohort of patients was 73.5±17.5%. In 50 subjects, the stenosis was bilateral with an average lumen narrowing of 75.8±20.1% on the main side and of 66.3±13.5% on the secondary side. Serum creatinine was 1.62±1.08 mg/dl in monolateral and 2.06±1.50 mg/dl in bilateral disease.

The stenosis was proximal in 79.2%, ostial in 6.3% and distal in 14.6% of cases. Vascular disease in other areas was present in 139 patients. Revascularization was performed up to and including 1992 only by angioplasty, and by endovascular stent only from 1998. Both simple angioplasty and stents were used in the interval years.

Statistical analysis

Data are shown as means±SD. Continuous variables were compared with analysis of variance (ANOVA) and t-tests. Non-parametric tests were used on discrete variables with non-normal distribution. For the follow-up study, primary end-points chosen for statistical analysis were cardiovascular death and starting of dialysis for ESRD. As a secondary end-point, we analysed increases in serum creatinine more than one-third of the basal value. Cox regression was employed for univariate and multivariate analysis.

Putative predictors of the chosen end-points were first analysed separately, and then all predictors with a statistical significance of P < 0.1 were simultaneously entered in a joint model (backward stepwise procedure). Differences in survival, obtained with the Kaplan–Meier method, were compared with the log-rank test.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Gender (M/F)</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>Diabetes (n)</th>
<th>Smokers (n)</th>
<th>Serum creatinine (mg/dl)</th>
<th>Serum cholesterol (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>65.6±11.2</td>
<td>143/52</td>
<td>163.8±22.2</td>
<td>91.2±15.2</td>
<td>28</td>
<td>106</td>
<td>1.74±1.22</td>
<td>214.7±46.2</td>
</tr>
</tbody>
</table>

*Smokers+ex-smokers.

Values are expressed as means±SD.
Results

Follow-up and survival in the entire cohort

The average follow-up was 54.4 ± 40.4 months (range 12–189). Five patients were lost to the follow-up. Of the patients who underwent revascularization, 19 had an angiographically proven restenosis of the renal artery. At the end of the observation, systolic blood pressure was reduced by 16.5 ± 25.6 mmHg and diastolic blood pressure by 9.1 ± 13.8 mmHg. During the observation period, a symptomatic, non-fatal, heart disease (angina, myocardial infarction or congestive heart failure) was recorded in 97 subjects, and 46 patients died of a cardiovascular complication. The mean survival time was 144.9 ± 21.9 months (SE) in the whole group.

In 41 patients, serum creatinine increased by more than one-third from baseline, and regular dialysis was started for ESRD in 20 patients. Mean dialysis-free survival was 154.1 ± 20.9 months.

Results of different treatments

There were 136 cases of patients treated invasively, and 54 subjects that were maintained on a medical treatment. The clinical characteristics of the two groups were comparable, although the number of patients on statins was higher in the medical group (Table 2).

Dialysis for ESRD was eventually necessary in 13 patients treated invasively and in seven treated medically. The mean change in serum creatinine was 1.29 ± 2.83 mg/dl in patients treated medically and 0.48 ± 2.20 mg/dl in those treated invasively (t = 4.242, P = 0.041). The analysis restricted to patients whose renal function did not worsen to ESRD showed an increase in serum creatinine of 0.26 ± 0.93 mg/dl, with increases of 0.51 ± 0.97 mg/dl in the revascularization group and 0.21 ± 0.93 mg/dl in the medical group (Table 3). In the 20 patients who required dialysis because of end-stage renal failure (ESRF), the stenosis was bilateral in three patients and unilateral in 17. The reduction in blood pressure was greater in patients treated invasively (Table 3).

In patients treated medically, the survival was 136.2 ± 24.4 months, and in those treated invasively survival was 103.5 ± 5.5 (log rank test = 0.02, P = 0.875, NS).

Mean dialysis-free survival was comparable for the two groups: 123.4 ± 4.5 in the revascularization group and 185.1 ± 35.7 in the medically treated group (log rank test = 0.02, P = 0.896, NS).

Survival analysis

To assess the risk factors for mortality, we applied the Cox regression analysis with the following variables: age, sex, smoking habit, diabetes, presence of vascular co-morbidity, total and low-density lipoprotein (LDL) cholesterol, baseline creatinine, hypertension, type and degree of stenosis (monolateral or bilateral, >75 or <75%), type of treatment (medical or invasive) and use of statins or ACEIs. We also analysed changes in serum creatinine and blood pressure as covariates varying over time. Antihypertensive drugs other than ACEIs were also analysed, but they showed no effect either singly or in combination.

The variables were first entered into the univariate regression analysis and those selected (P < 0.1) were analysed with multivariate analysis. This model produced two significant factors, which were the use of ACEIs and the change in serum creatinine. ACEI treatment induced a hazard ratio of 0.24 [95% confidence interval (CI) 0.08–0.71, P = 0.0098], and the change in serum creatinine produced a ratio of 1.62 (95% CI 1.04–1.82). Vascular co-morbidity was significantly associated in the univariate model (P = 0.054) but not in the multivariate model.

The Kaplan–Meier survival for patients treated or not treated with ACEIs produced a significant log rank test: 9.07, P = 0.0026 (Figure 1). The multivariate analysis with the same factors was repeated separately for patients treated medically (30.1% on ACEIs) or invasively (38.8% on ACEIs). The regression analysis confirmed a positive effect of ACEI treatment on survival. The effect was more significant in patients treated medically (P = 0.015) than in those treated invasively (P = 0.05). The survival over 50 months in survivors was 128.4 ± 4.3 months in the invasive

### Table 2. Clinical characteristics of patients given revascularization or medical treatment

<table>
<thead>
<tr>
<th></th>
<th>Medical (54)</th>
<th>Invasive (136)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67.9 ± 7.4</td>
<td>64.7 ± 12.2</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>159.7 ± 17.4</td>
<td>165.7 ± 24.1</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>88.9 ± 9.9</td>
<td>92.6 ± 17.2</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.69 ± 0.75</td>
<td>1.76 ± 1.39</td>
<td>NS</td>
</tr>
<tr>
<td>Stenosis (%)</td>
<td>70.4 ± 19.6</td>
<td>74.3 ± 16.7</td>
<td>NS</td>
</tr>
<tr>
<td>Bilateral stenosis</td>
<td>12 (21.2%)</td>
<td>38 (28%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes (n)</td>
<td>5 (9.2%)</td>
<td>23 (16.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking (n)</td>
<td>23 (42.5%)</td>
<td>90 (66.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>ACEIs (n)</td>
<td>21 (38.8%)</td>
<td>41 (30.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Statins (n)</td>
<td>17 (31.4%)</td>
<td>24 (17.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>219.2 ± 53.8</td>
<td>212 ± 42.7</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>157 ± 49.3</td>
<td>151.5 ± 48.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Table 3. Revascularization and medical treatment of atherosclerotic renal artery stenosis: long-term results

<table>
<thead>
<tr>
<th></th>
<th>Medical</th>
<th>Invasive</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (change)</td>
<td>−10.9 ± 8.5</td>
<td>−21.9 ± 10.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>DBP (change)</td>
<td>−7.7 ± 4.1</td>
<td>−10.4 ± 6.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ESRD (n)</td>
<td>7</td>
<td>13</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>+1.29 ± 2.83</td>
<td>+0.48 ± 2.20</td>
<td>0.041</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>+0.51 ± 0.97</td>
<td>+0.21 ± 0.93</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Excluding patients that evolved to ESRD.
group, 159.4±28 in the medical group (NS), 211.7±34.5 in patients on ACEIs, and 123.5±4.5 in patients not on ACEIs (NS).

End-stage renal failure

The same variables were employed in the analysis of risk for ESRF. In this case, the multivariate analysis produced only baseline serum creatinine as a predictor of ESRD. An abnormal serum creatinine carried a hazard ratio for ESRF of 1.66 (95% CI 1.22–2.26, \(P = 0.001\)).

Impairment of renal function (increase of serum creatinine of more than one-third)

The multivariate analysis revealed two factors. The first, an abnormal baseline serum creatinine (≥1.6 mg/dl), was a significant predictor of impairment with a hazard ratio of 1.42 (95% CI 1.03–1.95, \(P = 0.028\)). The second, the use of ACEIs, was associated with a reduced risk with a hazard ratio of 0.29 (95% CI 0.09–0.92, \(P = 0.036\)). The Kaplan–Meier analysis of survival time, free of confounding by serum creatinine, revealed a significant difference between subjects treated with ACEIs and those not treated (log rank test = 6.75, \(P = 0.009\)) (Figure 2).

Discussion

Our study, a long-term follow-up in a relatively large cohort of patients, was undertaken to assess the relative benefits of different therapeutic approaches on ARVD. The present findings confirmed that ARVD carries a high risk of cardiovascular mortality and ESRF. This risk is not substantially modified by revascularization. We found that ACEI use was the only modifiable factor that seemed to improve outcomes. We also found a beneficial effect of revascularization on blood pressure. This finding is consistent with previous reports and there is now widespread consent that the effect on blood pressure should be an expected result of revascularization [11,12].

We are fully aware that the unbalanced number of patients in the two groups (revascularization and medical treatment) is a weak point of this study. However, the similarity in clinical characteristics in the two groups and length of the follow-up strengthen our conclusions. In addition, our results support a recently published analysis that confirms the general benefits of renal revascularization [8]. Chabova et al. [13] conducted an observational study in medically treated patients with ARVD that was comparable in size with ours. In their patients, which had the same age range, a high cardiovascular risk and a modest deterioration in renal function were observed. We extended the observation period over 5 years, and in the follow-up there was no substantial difference between revascularization and medical treatments on the major end-points such as mortality or ESRD. The only exception, in terms of ESRD, was the impending occlusive bilateral disease. In this case, as was shown previously, revascularization can totally revert a poor renal prognosis [14]. We also confirmed that there is a lack of correlation between the degree of renal artery stenosis and baseline renal function or functional outcome [10].
The benefit on survival provided by ACEIs was demonstrated previously in a smaller group of patients with ARVD [15]. In the present study, which was longer and with a larger group, we confirmed this effect in both patients treated only medically and those who underwent revascularization. Furthermore, we extended these observations to renal function.

With respect to renal survival, we found less renal function impairment associated with the use of ACEIs. Unfortunately, we were not able to ascertain the number of patients who received this type of drug before ARVD diagnosis, nor for how long they received treatment. It is possible that some patients used drugs with protecting properties on renal function, which could explain why some patients evolved inexorably towards ESRD whereas others did not.

In patients who did not proceed to ESRD, we found that the change in serum creatinine during the observation was very modest, and that the benefits of revascularization over medical treatment at the end of the long follow-up were unimpressive.

This finding suggests that certain patients with ARVD are more prone to evolve to ESRD, and this is independent of therapeutic approach and obvious clinical characteristics of the patients. Renal size is a well known predictor of progression. It has already been demonstrated that prognosis is worse with reduced renal size [16]. In addition, the presence of already established renal parenchymal damage renders revascularization useless [17]. It is well known that at many levels there are major gaps in our understanding of the mechanisms and progression of ARVD [18].

We also observed an evolution towards ESRD in patients with normal renal size. Thus, these patients could be identified early in the course of their disease by using other criteria. We have already reported that carriers of the D allele of the ACE gene polymorphism had a higher mortality during ARVD [19]. Thus, an association of genetic factors with other clinical characteristics may cause this irreparable course of the disease.

The therapeutic arm of our study deals with ACE inhibition. We found that the use of ACEIs improved prognosis in both patient groups. This finding is of importance since this class of drugs is thought to increase the risk of serious worsening in renal function in ARVD, and there is great resistance to their use in these patients [20]. The administration of ACEIs in renovascular hypertension was wisely suggested years ago, because of their ability to control blood pressure and reduce vascular damage induced by hypertension [21]. Our present findings support and extend these indications. Given the extremely high cardiovascular mortality in ARVD, limiting the use of a drug known to protect the cardiovascular system deprives these patients with cardiovascular co-morbidities of a powerful therapeutic tool. The same applies to renal disease. The damage to renal parenchymal tissue associated with atherosclerotic renal artery stenosis is a target for ACEIs, and this mechanism may explain the minor changes in serum creatinine that were observed during ACEI use during both medical and invasive treatments.

Clearly, these drugs cannot be prescribed without due consideration, and there are risks associated with their use. Nonetheless, a close monitoring of ARVD patients, especially after revascularization, could reduce potential side effects of this drug. In addition, tighter control of all the factors negatively affecting prognosis, blood pressure, blood lipids and sodium state could completely change outcomes [22].

In conclusion, the present follow-up study based on a multiyear observation of patients with ARVD given revascularization or medical treatment showed that the prognosis of these patients was serious. No single therapeutic tool provided a superior overall beneficial effect. Although the invasive treatment alone did not significantly affect the outcome, combination with a tailored medical treatment, including ACEIs, may also improve the prognosis after revascularization.

Conflict of interest statement. None declared.

References
Factors affecting the long-term outcome in ARVD


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