Survival in Renal Vascular Disease

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Abstract. Renal artery stenosis (RAS) is a relatively uncommon but important potentially reversible cause of renal failure. Little is known about the natural history of ischemic renal disease secondary to RAS. In previous reports, these researchers examined the incidence and risk factors associated with RAS. The study presented here investigates the long-term follow-up of these patients, specifically the effect of RAS on 4-yr, all-cause mortality in a group of 1235 patients undergoing diagnostic cardiac catheterization and abdominal aortography. A total of 1235 consecutive patients undergoing cardiac catheterization also underwent an abdominal flush aortogram. Significant RAS was considered present if one or more renal artery had 50% or greater narrowing in luminal diameter. Four-year unadjusted survival for patients with RAS was 65% compared with 86% for patients undergoing catheterization without significant RAS. Factors associated with decreased 4-yr survival included increased age, increased serum creatinine, presence of RAS, peripheral vascular disease, congestive heart failure, diabetes, hypertension, and reduced ejection fraction. Using the Cox proportional hazards model, the factors associated with decreased 4-yr survival were the presence of significant RAS, reduced ejection fraction, elevated serum creatinine, and symptoms of congestive heart failure. These observations indicate that the presence of significant RAS is a strong independent predictor of 4-yr survival in this patient population. (J Am Soc Nephrol 9: 252–256, 1998)

Renal artery stenosis (RAS) is a relatively uncommon but potentially reversible cause of renal failure (1–4). The precise frequency of renal artery disease as a cause of end-stage renal disease (ESRD) has been difficult to determine accurately. RAS is frequently associated with generalized arterial disease. In recent years, technological advances have resulted in considerable improvements in transluminal and surgical techniques of revascularizing ischemic kidneys (5–7). To determine the potential therapeutic role for these techniques in the treatment of RAS, it is necessary to define the prevalence of RAS and the associated long-term outcome. We have reported previously the incidence of RAS and its major risk factors in a cohort of patients undergoing diagnostic cardiac catheterization (8). We now report the outcome of these patients after 4 yr of follow-up and specifically evaluate the impact of RAS on survival.

Materials and Methods

Patient Population

During a 5-mo period, 1305 of 1651 consecutive patients undergoing elective diagnostic cardiac catheterization at Duke University Medical Center were screened for the presence of renal artery disease through the use of single-plane abdominal aortography. Demographic data, medical history, physical findings, and blood chemistries were prospectively entered into a computerized medical information system before cardiac catheterization. Peripheral vascular disease was defined as a history of claudication; previous vascular procedure; a history of stroke or transient ischemic attack; or physical exam evidence of carotid, femoral, or abdominal bruits. Symptoms of congestive heart failure were classified in accordance with the New York Heart Association criteria. Hypercholesterolemia was defined as a total cholesterol elevated to >200 mg/dl. Hypertension was defined as diastolic BP >90 mmHg before catheterization. Hypertension was also considered present if the patient was taking antihypertensive medications.

Angiographic Methods

Coronary angiography was performed via the femoral artery approach by the Judkins technique. Coronary artery lesions graded as ≥75% narrowing of the luminal diameter were classified as significant. For the purposes of survival analysis, the severity of coronary artery disease (CAD) was graded according to the CAD prognostic index (9). After left ventriculography, the pigtail catheter was withdrawn into the abdominal aorta and positioned a few centimeters superior to the renal arteries. Aortography was performed in the anterior-posterior projection with nonionic contrast, power-injected at a rate of 20 ml/min to a total volume of 30 to 40 ml. The injection was recorded on 35-mm cine film at 30 frames per second for later analysis.

Aortographic Analysis

Aortograms were reviewed by a single observer blinded to the clinical information. The results of the aortogram and the presence or absence of renal artery disease were recorded. By convention, an

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angiographically significant lesion was defined as ≥50% luminal diameter narrowing of a major renal artery. Accessory renal arteries with disease were believed to be significant if more than one-third of the renal mass was estimated to be supplied by the vessel. Lesion location was classified as ostial, main artery, or branch vessel. Ostial lesions were defined as stenotic if the segment of the renal artery lumen immediately contiguous with the aorta was compromised. Lesions of the main segment of the renal artery began at least 2 to 3 mm beyond the ostial segment. Branch lesions were defined as stenotic lesions originating beyond the first bifurcation of the renal artery. The stenotic lesions were designated as atherosclerotic if they did not demonstrate the distinctive string-of-beads appearance characteristic of fibromuscular hyperplasia. No complications related to the aortogram were observed.

Follow-Up

Eight hundred and ninety-six patients were prospectively followed by the Duke Databank for Cardiovascular Disease. Follow-up information was collected using mailed questionnaires at 6 mo, 1 yr, and then yearly. Patients who did not respond to the questionnaire were contacted by telephone by trained interviewers. Data were recorded regarding survival status, the development of cardiac events, and rehospitalization. For patients who died, death certificates, as well as physician and hospital records (including autopsy information when available), were obtained, and we conducted telephone interviews with the next-of-kin to discuss the circumstances of the patient's death. In addition to the manner of death, it was also noted whether the patient had developed ESRD before death. All deaths were classified by an independent events committee (blinded to baseline information).

A National Death Index search was performed in November of 1995 on 339 patients not followed by the Databank for Cardiovascular Disease (because of insignificant CAD) and the 33 patients (3.6%) who had been considered lost to follow-up (10). Copies of their death certificates and hospital discharges were also obtained. These patients were also subsequently classified according to cause of death and the development of ESRD, as described above.

Statistical Analyses

Survival analysis was assessed using the Cox proportional hazards model. Patients were stratified into groups according to the presence or absence of significant RAS. All statistical analyses were performed using the Statistical Analysis System computer software package (SAS, Inc., Cary, NC.). All measured baseline variables (*vide supra*) were initially included in the model. Model selection was performed by a backward selection procedure. Only variables that achieved a level of significance of 0.05 in the multivariable model were included in the final model. We also tested for the presence of specific covariate interactions, including the effect of race on sex and the presence of CAD on the presence of RAS.

Results

We have reported previously on the incidence and predictors of RAS. In brief, we identified significant unilateral RAS in 11% and bilateral RAS in 4% of patients. By multivariate logistic regression, age, number of coronary vessels with significant disease, presence of congestive heart failure, female sex, and presence of peripheral arterial disease were all independently associated with significant RAS (8).

Patient Survival

Two hundred and nineteen patients (17.1%) died during follow-up. The death certificates were available on all but two of these patients. The 4-yr survival of patients without significant RAS was 88% compared with 67% for patients with significant RAS (Figure 1). Table 1 depicts the variables by univariate analysis that were associated with increased mortality. The presence of significant renal arterial disease, increased age, congestive heart failure, severity of CAD, peripheral arterial disease, increased serum creatinine, and the presence of diabetes were all associated with increased mortality. By multivariable analysis, significant RAS, decreased ejection fraction, increased serum creatinine, and the presence of symptomatic congestive heart failure were all associated with increased mortality (Table 2). The previously outlined covariate interactions did not appear to have a significant effect in the model. Figure 2 demonstrates the Kaplan–Meir survival curves for patients with and without significant RAS, adjusted for all of the measured baseline variables (except RAS). The adjusted survival of patients without RAS was 93% compared with 87% for patients with RAS. Thus, it appears that significant RAS has had a highly significant impact on long-term survival, independent of differences in other measured variables. The majority of deaths in both groups were secondary to cardiovascular disease: 69% in patients with RAS compared with 78% in the group without RAS.

Seven hundred and fifty-three of the 896 patients prospectively followed had no significant RAS, of which 104 (13.8%) developed a myocardial infarction, 56 (7.4%) underwent percutaneous transluminal angioplasty (PTCA), and 196 (25.7%) underwent coronary artery bypass grafting (CABG). One hundred and forty-three of the prospectively followed patients had significant RAS, of which 44 (31%) developed a myocardial

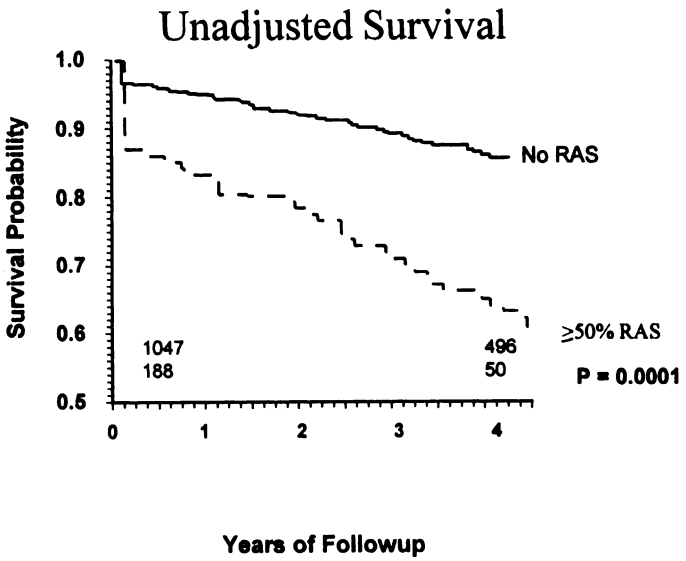

Figure 1. Kaplan–Meir survival curve for 4-yr survival stratified according to the presence or absence of significant renal artery stenosis (RAS). The numbers along the x-axis represent patients remaining in analysis at each time point.

Table 1. Clinical and catheterization-derived variables with associated hazard ratio (with 95% confidence interval) from Cox model[a]

Variable	Risk Ratio	*P* Value
>50% renal artery stenosis	2.0 (1.5 to 2.8)	0.0001
Mean age[b]	2.3 (1.8 to 3.0)	0.0001
Congestive heart failure	1.3 (1.7 to 5.6)	0.0001
Ejection fraction[c]	1.7 (1.5 to 2.1)	0.0001
CAD index[d]	1.1 (1.1 to 1.2)	0.005
Peripheral vascular disease	2.3 (1.3 to 3.8)	0.0020
Creatinine[e]	1.8 (1.3 to 2.4)	0.002
Diabetes mellitus	1.7 (1.2 to 2.6)	0.009
Hypertension	1.4 (1.0 to 2.1)	0.04
Female	1.4 (1.04 to 2.1)	0.08
White	1.3 (0.9 to 1.9)	0.1
Smoking	1.2 (0.8 to 1.7)	0.2
Hyperlipidemia	1.0 (0.9 to 1)	0.5
History of CAD	1.0 (0.6 to 1.4)	0.8

[a] *P* values are for univariate Cox proportional hazards model for survival. CAD, coronary artery disease.
[b] Analyzed by 10-yr increments.
[c] Analyzed by 10% change.
[d] Analyzed for 10-U change.
[e] Analyzed for 1-mg change.

Table 2. Clinical and catheterization-derived variables from multivariable Cox model with associated hazard ratio (with 95% confidence interval)[a]

Variable	Risk Ratio	*P* Value
Renal artery stenosis	2.9 (1.7 to 7)	0.0001
Ejection fraction[b]	1.7 (1.2 to 2.2)	0.0002
Creatinine	1.3 (1.1 to 1.5)	0.02
Congestive heart failure	2.4 (1.3 to 4.1)	0.0021

[a] The data represent a multivariate analysis.
[b] Analyzed for 10% change.

infarction, 14 (26.3%) underwent PTCA, and 46 (32%) underwent CABG. Ninety-five percent of the CABG, PTCA, and myocardial infarction events occurred within the first 2 mo after catheterization.

Four patients had end-stage renal failure listed on their death certificates at the time of death. Of these, one had ESRD at baseline examination and one had significant bilateral RAS and a serum creatinine of 1 at baseline evaluation. The other two had insignificant RAS and renal insufficiency at baseline.

Discussion

In this study, we followed 1235 patients for more than 4 yr and studied the effect of incidentally discovered significant RAS on long-term survival. The 4-yr survival of patients with RAS was 67% compared with 88% for patients without significant RAS (Figures 1). Patients with RAS were more likely to have significant CAD and decreased ejection fraction than

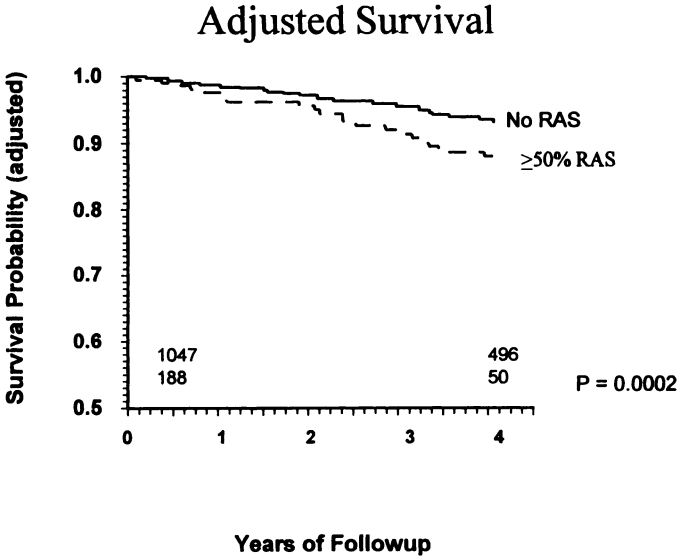

Figure 2. Adjusted Kaplan–Meir survival curve stratified for the presence or absence of significant RAS. Curves have been adjusted for age, presence of peripheral arterial disease, congestive heart failure, serum creatine, smoking, sex, hypertension, race, diabetes, history of coronary artery disease (CAD), hyperlipidemia, severity of CAD, and ejection fraction. The numbers along the x-axis represent patients remaining in analysis at each time point.

patients without RAS. Even when adjustments were made for differences in baseline characteristics between the groups, the presence of RAS continued to have an impact on mortality (Figure 2). The major cause of death among patients with or without significant RAS was cardiovascular disease. However, among patients who died, it was quite uncommon for patients to have progressed to ESRD. These data suggest that RAS contributed to, but was only a secondary cause of, death in these patients.

Valentine *et al.* studied a large group of patients undergoing abdominal aortography as preoperative evaluation for patients with abdominal aortic aneurysm disease (11). They noted a very strong association between the presence of asymptomatic RAS and the presence of clinically overt CAD. In addition, they also noted that the presence of asymptomatic renal artery disease was even more predictive of both early and late perioperative myocardial infarction and death than was the presence of clinically overt CAD (11). In a joint study of patients attending the Glasgow and Newcastle Hypertension clinics, Isles and colleagues noted that the 5-yr survival of patients with RAS was 83% compared with 90% for patients with essential hypertension, with death occurring mainly from coronary or cerebrovascular disease rather than renal failure (12). A similar reduction in survival to 67% at 5 yr compared with 92% in the general population has been reported by Wollenweber *et al.* (13). Thus, although renovascular disease frequently progresses, death often occurs from progression of coronary or cerebrovascular disease before a decline in renal function.

A number of studies have reported the outcome of renal artery revascularization procedures by either surgical tech-

niques or transluminal angioplasty with or without deployment of a metallic stent. The group from the Mayo Clinic reported a 4-yr survival rate for patients who underwent renal artery angioplasty (14) of 65%, and the majority of the deaths in their series was from cardiovascular causes.

An intervention to decrease the rate of progression of both the renal artery lesion and the decline in renal function in an individual kidney would appear attractive. At present, however, there are no prospective randomized trials that support either surgical or percutaneous intervention demonstrating improved longevity or a reduction in rate of decline in renal function over a "wait-and-see approach." The decision to perform angioplasty in a kidney with 60% or greater RAS would appear reasonable because the likelihood of progression is high. If surgery or angioplasty is to be performed in such circumstances, it would be wise to evaluate the patient for other cardiovascular disease because the probability of death from a cardiovascular event is far greater than the risk of the patient developing ESRD.

Kidneys with significant RAS produce increased amounts of renin and angiotensin (15). These hormones have a number of hemodynamic effects, most notably the vasoconstrictor effect of angiotensin II, with resultant systemic hypertension. However, angiotensin II is not only a potent vasoconstrictor, but it also likely stimulates cellular hypertrophy and proliferation (16,17). High levels of angiotensin II likely contribute to vascular and ventricular hypertrophy (18), accelerate atherosclerosis (19), and are associated with progressive glomerular sclerosis independent of the associated hemodynamic effect. The increased mortality observed in patients with significant RAS may be the result of excessive angiotensin.

The level of RAS that should be considered clinically significant has not been clearly defined. Many studies that have examined the epidemiology of RAS have chosen a 50% cutoff level of significant RAS (20–24). A recent study has chosen 50% RAS as the level at which renal revascularization procedures were performed. Significant improvements in BP were observed with renal angioplasty and stenting at 50% stenosis (25). Surgical studies of renal revascularization have, in general, chosen higher levels of stenosis. It should be pointed out, however, that the assessment of the percentage stenosis in single-plain views of renal arteries is somewhat arbitrary.

This study selected patients for inclusion by virtue of their presentation with some manifestation of perceived CAD. Clearly, these observations cannot be generalized to the total number of patients with renal vascular disease. However, it should be pointed out that the demographics of the patients in this study do not appear to differ that much from previously reported studies of atherosclerotic renal artery disease (22–24). Almost every study to date has documented the frequent association of renal arterial disease with significant coronary artery and peripheral vascular disease.

This study has a number of limitations. First, abdominal aortography was used to evaluate RAS. Selective renal artery catheterization may have identified disease not observed here. Abdominal aortography is likely relatively specific, but may not be particularly sensitive for the detection of ostial lesions, however. Second, we do not have prospective information concerning mortality in approximately one-third of the patients. The National Death Index survey, however, has been reported to be an accurate method for identifying patients who died with an accuracy of greater than 90% (10). We did not have prospective data on the development of ESRD in this group of patients, although we believe it highly unlikely that a significant number of patients may have developed ESRD and were on dialysis treatment. Given the annual mortality of this group of patients of greater than 25%, we believe that if this were the case we would have identified them from our examination of their death certificates and medical records. Finally, we were unable to examine the effect of renal revascularization on subsequent mortality in this group of patients, because, of the patients we prospectively followed and based on an examination of medical records of those that died, none appeared to have undergone such a procedure. This study was initiated before the recent increased usage of percutaneous renal revascularization.

In conclusion, patients with RAS are at increased risk of death from cardiovascular disease. Whether improvement in renal artery perfusion will affect long-term survival is unclear at this stage.

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