Impact of incidental renal artery stenosis on long-term mortality in patients with peripheral arterial disease undergoing vascular procedure

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Objective: **In peripheral arterial disease (PAD), mortality is high. Incidental renal artery stenosis (RAS) is a predictor of mortality in PAD patients undergoing angiography. This might be relevant for risk-benefit assessment when vascular surgery is considered, both in terms of perioperative risk, and in terms of life expectancy.**

Methods: **We studied the prognostic impact of incidental RAS in 488 subjects (334 men, 154 women; mean follow-up 6.0 ± 3.4 years) who underwent angiography for PAD in a single center between 1997 and 2000. Renal arteries were visualized and follow-up data concerning vascular procedures were analyzed.**

Results: **RAS (diameter reduction >50%) was present in 26%. Forty-six percent of study patients underwent a vascular procedure (85% vascular surgery, remainder underwent amputation). Patients that underwent vascular surgery had a better renal function at baseline, less history of stroke, and a larger proportion of smokers. Overall mortality was similar for patients that underwent surgery (54.5%) and those without surgery (49.6%). There was no difference in 90-day postoperative mortality for patients without or with RAS (7.2% vs 10.3%; NS). For subjects that underwent bypass surgery, long-term mortality was substantially and significantly higher among those with RAS (65.1%) vs those without RAS (43.5%). On Cox regression analysis, age was the only independent predictor of 90-day postoperative mortality. The well-known cardiovascular risk factors of age, diabetes mellitus, history of prior peripheral vascular disease, smoking, prior myocardial infarction, prior stroke, and amputation, as well as presence of RAS, were independent predictors for overall mortality.**

Conclusion: **In PAD, incidental RAS predicts long-term mortality independent of other risk factors. The elevated mortality is not due to a higher postoperative risk. Subjects presenting with PAD and RAS can therefore undergo vascular procedures with the same risk as other patients.** **(J Vasc Surg 2011;54:785-90.)**

In patients with peripheral arterial disease (PAD), mortality is high[1-3] and is most likely related to the clustering of cardiovascular risk factors in these patients. When renal function impairment is simultaneously present, mortality is even higher.[4] Renal artery stenosis (RAS) is frequently encountered as an incidental finding in patients undergoing routine angiography for PAD, with prevalence between 5% and 40%.[5-7] We have previously demonstrated that incidental RAS is an independent predictor of a substantially elevated mortality in PAD patients.[6] The hypothesis is that patients with incidental RAS have a higher mortality due to higher postoperative risk. This might be relevant for risk-benefit assessment when vascular surgery is considered, both in terms of perioperative risk, and in terms of life expectancy. Therefore, we investigated the prognostic impact of incidental RAS for long-term mortality as well as perioperative mortality in a cohort of consecutive subjects who underwent intra-arterial digital subtraction angiography (DSA) for PAD in a single center between 1997 and 2000, and were treated either conservatively or by vascular intervention, depending on clinical assessment.

METHODS

Design of the study. For the cohort[6] of 550 consecutive patients described previously, with clinically confirmed PAD by noninvasive examinations (ie, ankle-brachial index or duplex ultrasound of the lower extremities), patient records were reviewed, and detailed additional data regarding vascular procedures were extracted. Briefly, these were subsequent patients, diagnosed between 1997 and 2000. For the current study, follow-up for mortality (in the previous report until 2004) was extended until January 1, 2008, amounting to a mean follow-up time of 6 years. All patients underwent angiography with the intention of surgical or radiological intervention from January 1997 to December 2000 in a single center, as judged by the vascular surgeons. Patients in whom the angiography did not allow proper assessment of the renal arteries were excluded from the analysis. A single reviewer (H.H.), blinded to patients' diagnoses and indications for the procedure, evaluated the

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Table I. Baseline clinical characteristics of 488 patients with and without vascular operation

Characteristic	*No operation (n = 264)*	*Operation (n = 224)*	P	*Odds ratio (95% confidence interval)*
Age (years; mean ± SD)	66.4 ± 11.5	65.7 ± 11.2	.54	
Male gender (% [n])	63.3 (167)	74.6 (167)	.07	
Overall mortality (% [n])	49.6 (131)	54.5 (122)	.29	1.21 (0.85-1.74)
RAS (% [n])	26.5 (70)	25.9 (58)	.88	0.97 (0.65-1.45)
GFR (mL/min per 1.73 m^2; mean ± SD)	71.4 ± 25.0	80.3 ± 26.4	<.0001	
- GFR in patients with no RAS	76.0 ± 23.6	83.7 ± 25.3	.003	
- GFR in patients with RAS	58.4 ± 24.1	70.6 ± 27.4	.008	
History of hypertension (% [n])	58.7 (155)	57.8 (129)	.85	0.97 (0.67-1.39)
History of diabetes (% [n])	29.5 (77)	32.1 (72)	.53	1.13 (0.77-1.67)
History of myocardial infarction (% [n])	20.8 (55)	25.4 (57)	.23	1.30 (0.85-1.98)
History of stroke (% [n])	20.1 (53)	13.4 (30)	.05	0.62 (0.38-1.003)
History of smoking (% [n])	57.5 (145)	67.1 (147)	.033	1.51 (1.03-2.20)
History of previous PAD (% [n])	31.4 (83)	37.5 (84)	.16	1.31 (0.90-1.90)

GFR, Glomular filtration rate; *PAD,* peripheral arterial disease; *RAS,* renal artery stenosis.

angiograms for the presence of renal artery stenosis. A diameter reduction of >50% was considered diagnostic for the presence of RAS; severe stenosis was considered to be present when the stenosis exceeded 75%.[8] Clinical data, including surgical or radiological procedures, were obtained from patient records and mortality data (until January 1, 2008) were obtained from the hospital information system. The Institutional Review Board approved this study.

Definitions. Hypertension was defined according to the 2007 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension,[9] prescription of antihypertensive medications, or a clinical history of hypertension. A patient was classified as having diabetes if there was a clinical history of diabetes or if the patient was taking insulin or oral antidiabetic agents. We used the abbreviated Modification of Diet in Renal Disease (MDRD) equation advocated in the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines[10] to estimate glomerular filtration rate (GFR).

Baseline characteristics. Eight clinical variables were recorded at baseline (ie, time of angiography): the serum creatinine before angiography; a history of myocardial infarction; a history of stroke; diabetes mellitus (present or absent); smoking history (ever/stopped or never); history of prior PAD (ie, previous treatment either conservative or not otherwise specified); history of hypertension; and current blood pressure at time of angiography.

Vascular procedures. Vascular procedures were defined as either a surgical procedure (ie, primary vascular bypass operation or amputation) or endovascular treatment (ie, revascularization with primary percutaneous transluminal angioplasty).

Statistical analysis. Comparisons between groups (renal artery stenosis vs nonrenal artery stenosis) on baseline variables were performed using Pearson χ^2 test. Survival was assessed by Kaplan-Meier curves, and to test for independent predictors of mortality, multivariate analysis was performed using single-step Cox regression analysis. The renal function was classified according to the cut-offs recommended in the KDOQI criteria[10] for defining moderate (GFR 30-60 mL/min/1.73 m^2) and severe (GFR <30 mL/min/1.73 m^2) renal function impairment. All statistical analyses were performed in SPSS 14.0 for Windows (SPSS, Chicago, Ill). Statistical significance was defined as a *P* value <.05.

RESULTS

From January 1997 to December 2000, 550 consecutive angiograms were performed in patients, all with confirmed PAD. The renal arteries could be assessed in their entirety for renal artery stenosis (diameter reduction >50%-75% and ≥75%) in 499 angiograms. The reasons for incomplete visualization of the renal arteries were technical. Of the 499 evaluable patients, 11 patients could not be included because of incomplete clinical data. Atherosclerotic renal artery stenosis was present in 128 (26%) of the 488 patients; of these patients, 35 (27%) had a luminal renal artery stenosis of more than 75%, and 73 (57%) had a bilateral renal artery stenosis.

Baseline characteristics of the population are presented in Table I, by a break-up according to whether or not surgery was performed. Of the 224 patients that underwent a vascular procedure, 190 (85%) had vascular surgery; the remainder underwent an amputation. Patients that underwent vascular surgery had a better renal function at baseline, less history of stroke, and a larger proportion of smokers, suggesting impact of patient selection for surgery. Long-term mortality was similar for patients that underwent surgery (54.5%) and those without surgery (49.6%). Table II shows the baseline characteristics of patients who underwent percutaneous transluminal angioplasty (PTA) compared with vascular surgery. There was no difference in short-term mortality; only long-term mortality was slightly elevated in patients who underwent vascular surgery. There was no difference in the renal function or the other risk factors between the groups. Patients with RAS were older and had a higher prevalence of cardiovascular risk factors (Table III). In Table IV, mortality data are presented by a break-up by presence or absence of RAS, for patients that

Table II. Baseline clinical characteristics of 366 patients who underwent PTA or vascular operation

Characteristic	*PTA (n = 142)*	*Operation (n = 224)*	P	*Odds ratio (95% confidence interval)*
Age (years; mean ± SD)	64.7 ± 12.5	65.7 ± 11.2	.44	
Male gender (% [n])	61.3 (87)	74.6 (167)	.007	
Overall mortality (% [n])	43.7 (62)	54.5 (122)	.044	1.54 (1.01-2.36)
90-day postoperative mortality (% [n])	4.2 (6)	8.0 (18)	.151	1.98 (0.77-5.12)
1-year postoperative mortality (% [n])	11.3 (16)	14.3 (32)	.41	1.31 (0.69-2.49)
RAS (% [n])	22.5 (32)	25.9 (58)	.47	1.20 (0.73-1.97)
GFR (mL/min per 1.73 m^2; mean ± SD)	75.2 ± 23.5	80.3 ± 26.4	.06	
- GFR in patients with no RAS	78.5 ± 22.7	83.7 ± 25.3	.86	
- GFR in patients with RAS	63.6 ± 22.8	70.6 ± 27.4	.22	
History of hypertension (% [n])	55.6 (79)	57.8 (129)	.68	1.09 (0.72-1.67)
History of diabetes (% [n])	27.1 (38)	32.1 (72)	.31	1.27 (0.80-2.03)
History of myocardial infarction (% [n])	20.4 (29)	25.4 (57)	.27	1.33 (0.80-2.21)
History of stroke (% [n])	14.1 (20)	13.4 (30)	.85	0.94 (0.51-1.74)
History of smoking (% [n])	64 (87)	67.1 (147)	.54	1.15 (0.73-1.80)
History of previous PAD (% [n])	28.2 (40)	37.5 (84)	.066	1.53 (0.97-2.41)

GFR, Glomular filtration rate; *PAD,* peripheral arterial disease; *PTA,* percutaneous transluminal angioplasty; *RAS,* renal artery stenosis.

Table III. Baseline clinical characteristics of patients with and without renal artery stenosis

Characteristic	*No RAS (n = 360)*	*RAS (n = 128)*	P	*Odds ratio (95% confidence interval)*
Age (years; mean ± SD)	64 ± 11	71 ± 10	<.0001	
Overall mortality (% [n])	44.2 (159)	73.4 (94)	<.0001	3.50 (2.24-5.49)
History of hypertension (% [n])	53.8 (193)	71.1 (91)	.001	2.12 (1.37-3.27)
History of diabetes (% [n])	27.5 (98)	39.8 (51)	.009	1.75 (1.15-2.67)
History of myocardial infarction (% [n])	19.4 (70)	32.8 (42)	.002	2.02 (1.29-3.18)
History of stroke (% [n])	15.0 (54)	22.7 (29)	.048	1.66 (1.00-2.75)
History of smoking (% [n])	65.9 (228)	51.2 (64)	.004	0.54 (0.36-0.82)
History of previous PAD (% [n])	30.6 (110)	44.5 (57)	.004	1.83 (1.21-2.76)
GFR (mL/min per 1.73 m^2; mean ± SD)	79.6 ± 24.7	63.9 ± 26.2	<.0001	

GFR, Glomular filtration rate; *PAD,* peripheral arterial disease; *RAS,* renal artery stenosis.

Table IV. Long-term mortality and postoperative mortality for patients with or without vascular surgery according to the presence or absence of renal artery stenosis

	No RAS (n = 360)	*RAS (n = 128)*	P
No operation (n = 264)	4.7% (79/194)	74.3% (52/70)	<.0001
All operation (n = 224)	48.2% (80/166)	72.4% (42/58)	.001
- Bypass operation (n = 190)	43.5% (64/147)	65.1% (28/43)	.013
- Amputation (n = 34)	84.2% (16/19)	93.3% (14/15)	.412
90-day postoperative mortality (% [n])	7.2 (12)	1.3 (6)	.45
1-year postoperative mortality (% [n])	13.3 (22)	17.2 (10)	.56

RAS, Renal artery stenosis.

underwent surgery and those who had not. Among the patients that underwent surgery, mortality was extremely high for those with RAS and similar for those with or without RAS that underwent amputation. For subjects that underwent bypass surgery, mortality was substantially and significantly higher among those with RAS (65.1%) versus those without RAS (43.5%). There were no differences, however, in 90-day and 1-year postoperative mortality for patients with RAS as compared with no RAS, and there was no difference in mortality between patients with unilateral RAS versus bilateral RAS (Table V).

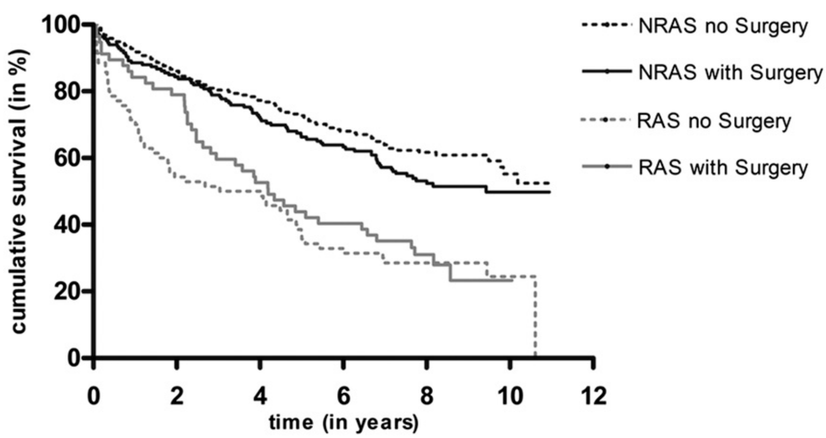
As shown by the Kaplan-Meier survival curves in the Fig, the estimated 5- and 10-year survival probability for patients who did not undergo a vascular procedure was 72% and 55%, respectively, for patients without RAS as compared with 36% and 24%, respectively, for patients with RAS. The estimated 5- and 10-year survival probability for patients with a vascular procedure in the group without RAS was 66% and 50%, respectively, versus 42% and 23%, respectively, in the group with RAS ($P < .0001$).

The independent contribution of the various risk factors for 90-day postoperative mortality and long-term mortality were assessed by Cox regression analysis, as shown in Table VI and VII, respectively. For the 90-day postoperative mortality, age was the only independent predictor ($P = .001$). The well-known cardiovascular risk factors age, dia-

Table V. Long-term mortality and postoperative mortality for patients with or without vascular surgery according to the presence of unilateral or bilateral renal artery stenosis

	Unilateral RAS (n = 55)	*Bilateral RAS (n = 73)*	P
No operation (n = 70)	82.4% (28/34)	66.7% (24/36)	.133
All operation (n = 58)	71.4% (15/21)	73% (27/37)	.90
- Bypass operation (n = 43)	70.6% (12/17)	61.5% (16/26)	.54
- Amputation (n = 15)	75% (3/4)	100% (11/11)	.086
90-days postoperative mortality (% [n])	9.5 (2)	10.8 (4)	.88
1-year postoperative mortality (% [n])	19 (4)	16.2 (6)	.46

RAS, Renal artery stenosis.



No. at risk

NRAS no Surg	194	167	149	132	120	107
NRAS with Surg	166	139	119	105	87	83
RAS no Surg	70	38	34	22	20	17
RAS with Surg	58	45	30	23	18	14

Fig. Kaplan-Meier survival plots for patients with peripheral arterial disease with and without surgery, comparing outcome for those without renal artery stenosis (*NRAS*) and with renal artery stenosis (*RAS*).

betes mellitus (DM), history of prior peripheral vascular disease (PVD), smoking, prior myocardial infarction, prior stroke, and amputation, as well as presence of RAS, were independent predictors for long-term mortality.

DISCUSSION

In our previous study, we demonstrated that the mortality in patients with PAD is extremely high, especially in patients with concomitant incidental RAS and PAD. As previously demonstrated, incidental RAS is an independent predictor of long-term mortality in patients with PAD.[6] In this study, we have examined the contribution of the perioperative mortality on the total (5- and 10-year) mortality. In contrast to our hypothesis or previous ideas,[11] this mortality was not influenced by the operative procedures, irrespective of the patient had a RAS or not. The 90-day and 1-year postoperative mortality was not significantly different in patients with and without RAS. In terms of life expectancy, patients with incidental RAS have higher mortality in comparison to patients without RAS; however, this is not due to postoperative short (90 days) or midterm (1 year) mortality.

The association between renal function and increased mortality in patients with PAD undergoing lower extremity bypass surgery has previously been described in this journal by O'Hare et al[12] and Owens et al.[4] The first study found that patients receiving dialysis have a high incidence of amputation within 1 year of lower extremity revascularization that is not explained by a higher prevalence of demographic characteristics and comorbid conditions. The second study demonstrated that in their cohort of 456 subjects, patients with more severe renal insufficiency had significantly higher mortality and lower amputation-free survival following lower extremity revascularization. The detrimental effects of reduced renal function are profound and begin well before the onset of dialysis. The overall 5-year survival in this cohort was 43%. This is comparable to ours, namely 42% in patients with RAS after a vascular procedure. One may deduce from our data that the increased mortality in the two above-mentioned studies is due to poor prognostic impact caused by incidental RAS. In contrast to the previously depicted studies, renal function was not a prognostic marker for mortality in our cohort. Patients with PAD who underwent vascular operation had

Table VI. Single-step Cox multivariate analysis of the predictors of 90-day postoperative mortality

	P	*Hazard ratio (95% confidence interval)*
Age	.001	1.09 (1.35-1.16)
History of hypertension	.46	1.39 (0.58-3.31)
History of diabetes	.72	1.18 (0.47-2.98)
History of myocardial infarction	.23	1.68 (0.72-3.88)
History of stroke	.43	1.50 (0.55-4.10)
History of smoking	.11	2.23 (0.84-5.91)
History of previous peripheral arterial disease	.21	1.74 (0.74-4.13)
Amputation	.31	1.79 (0.58-5.49)
PTA vs vascular bypass operation	.53	1.34 (0.50-3.83)
Glomerular filtration rate	.72	0.99 (0.98-1.02)
Renal artery stenosis	.93	1.04 (0.43-2.50)

PTA, Percutaneous transluminal angioplasty.

Table VII. Single-step Cox multivariate analysis of the predictors of long-term mortality

	P	*Hazard ratio (95% confidence interval)*
Age	.000	1.08 (1.06-1.10)
History of hypertension	.418	1.12 (0.85-1.48)
History of diabetes	.000	1.74 (1.31-2.30)
History of myocardial infarction	.002	1.55 (1.67-2.06)
History of stroke	.001	1.65 (1.22-2.25)
History of smoking	.000	1.73 (1.28-2.33)
History of previous peripheral arterial disease	.003	1.50 (1.15-1.97)
Amputation	.002	2.01 (1.29-3.12)
Glomerular filtration rate	.553	1.00 (0.99-1.01)
Renal artery stenosis	.024	1.39 (1.04-1.84)

better renal function compared with those who were not operated (Table I). The patients with PAD who did not undergo vascular surgery had comparable kidney function to those who underwent PTA (Table II). The question arises how this is to be explained. One can hypothesize that patients with the worst renal function had severe inoperable vascular lesions and thus operation was deemed too risky. In this respect, patients with RAS who went through amputation had the lowest estimated glomerular filtration rate (eGFR; 60.2 ± 18.2 mL/min/1.73 m^2). Another explanation may be preoperative selection bias by the initial physicians who determined whether the patient should be operated or not, based on renal function. Nevertheless, our data give us insight in the combined occurrence of RAS and renal function impairment as tools for preoperative risk-benefit assessment. Despite the high mortality associated with incidental RAS and renal insufficiency, they are not the cause of short- or long-term postoperative mortality. It may therefore be anticipated that all patients with surgical indication for vascular operation should be operated upon.

Some limitations of our study should be considered. Because this was a retrospective post hoc analysis, all liabilities associated with the retrospective nature of the study apply. The fact that 90-day postoperative mortality was not significant may be due to underpowering of this study to really discriminate in short-term mortality. However, as already mentioned, the primary aim was to evaluate the long-term mortality in patients with PAD and incidental RAS. Regrettably, nonfatal perioperative events and medication use were not recorded. The medication use especially can be of importance, since the data of this study were obtained starting back in 1997. In the past, many patients with PAD were not treated as aggressively as today, such as standard with statins, angiotensin-converting enzyme inhibitors, or rigorous antiplatelet therapy. With the knowledge of the medication use, it was possible to discriminate whether the patients in our study were treated according to the standards of current practice. Furthermore, we cannot rule out that more favorable patients were selected for surgery.

CONCLUSION

Incidental RAS predicts long-term mortality independent of other risk factors. RAS is a strong marker of a poor prognosis, manifested in increased mortality and inoperability in patients with PAD. Consequently, risk assessment in patients who undergo angiography should include visualizing the renal arteries and measurement of renal function. Despite the elevated mortality in subjects with RAS, the postoperative risk does not contribute to the amazing high total mortality, and therefore patients with PAD and RAS should not be withheld from vascular surgery.

AUTHOR CONTRIBUTIONS

Conception and design: KM, GN, AW
Analysis and interpretation: KM, CZ, GN, AW
Data collection: KM, HH, JB, AW
Writing the article: KM, CZ, GN, AW
Critical revision of the article: KM, CZ, GN, AW
Final approval of the article: KM, CZ, HH, JB, GN, AW
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